



Macedonian Journal of Anaesthesia

Anaesthesia / Resuscitation

Pain Management / Critical Care

VOL. 10 - NO. 3
SEPTEMBER 2026

JOURNAL OF THE MACEDONIAN SOCIETY
OF ANAESTHESIOLOGISTS AND THE
MACEDONIAN SOCIETY OF CRITICAL CARE MEDICINE

Publisher:

Department of Anesthesia and Reanimation, Faculty of Medicine
“Ss. Cyril and Methodius” University, Skopje, R. N. Macedonia

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I.V. Paracetamol

БЕЗБЕДНА АНАЛГЕЗИЈА

менаџирање на болка кога сте загрижени за безбедноста



I.V. paracetamol за прв пат во Европа е применет во 2001 година, а денес поради неговата докажана безбедност и ефикасност е прв од избор **аналгетик и антипиретик**.

Предоперативна и Интраоперативна Аналгезија:

Предоперативна аналгезија е дефинирана како третман кој што започнува пред оперативниот зафат се со цел да се превенира воспоставувањето на централна сензибилизација на болка.

i.v. paracetamol е безбеден, добро толериран лек со докажана ефикасност како **предоперативна и интраоперативна аналгезија** за умерена до средна болка при оперативни зафати.

Голем број на клинички студии ја докажуваат ефикасноста на i.v. paracetamol како **предоперативна и интраоперативна аналгезија**.

КЛИНИЧКА СТУДИЈА:

Ефект од **предоперативен i.v. paracetamol** за постоперативни аналгетски потреби кај пациенти кои се подложни на оперативни зафати. A Sreenivasulu, R Prabhavathi, 2015

Цел: Да се утврди ефикасноста на **предоперативната употреба на 1000mg i.v. paracetamol** кај постоперативните болки и аналгетски потреби кај пациенти подложни на хируршки зафати.

Метод: 60 пациенти беа поделени во две рандомизирани групи од по 30 пациенти.

На I. Група им беше администрирано ампула од 1000mg i.v. paracetamol разредена 0,9%NaCl p-ор 30 минути пред индукција (**ГРУПА П**),

На II. Група им беше администрирано i.v. 0,9% NaCl p-ор 100мл 30 минути пред индукција (**ГРУПА НС**)

Сите пациенти беа индуцирани со i.v. thiopentone 5mg/kg, i.v. fentanyl 2µg/kg, i.v. vecuronium 0.1mg/kg

Постоперативниот резултат на болка беше мерен со **Визуелна Аналогна Скала (ВАС)** од "0-10". Исто така беше забележувана и **постоперативната употреба на tramadol** како спасувачки аналгетик. Инциденцата на **постоперативно гадење и повраќање (ПОПГ)** и други компликации исто така беа забележувани во пост оперативниот период.

Резултатот на постоперативната болка беше забележуван во интервали 15 мин, 30 мин, 1 час, 2 часа, и 6 часа.

Заклучок: Предоперативна администрација на 1000mg i.v. paracetamol кај пациенти подложни на оперативен зафат обезбедува **статистички задоволителна аналгезија**, и ја **намалува постоперативната употреба на tramadol**. Оттука 1000mg i.v. paracetamol може безбедно да се администрира како превенција при оперативни зафати.

Резултат:

Табела 1: Споредба на средниот резултат на болка (ВАС) помеѓу двете групи

Интервали	I Група П	II Група НС	P вредност
15 мин	2.06 ± 0.63	2.61 ± 0.56	0.0006
30 мин	2.35 ± 1.17	3.84 ± 1.55	0.0001
1 час	2.42 ± 1.12	2.87 ± 0.99	0.0989
2 часа	2.13 ± 1.06	2.52 ± 0.89	0.1219
6 часа	2 ± 0.52	2.52 ± 0.89	0.0549

Табела 2: Споредба за потребите од tramadol помеѓу двете групи

Интервали	I Група П	II Група НС	P вредност
До 1 час	4 (12.90%)	15 (50%)	0.0002
1-2 часа	3 (9.68%)	2 (6.45%)	0.64
2-6 часа	1 (3.23%)	3 (9.68%)	0.301
Вкупно	8 (25.81%)	20 (64.52%)	0.002

Табела 3: Споредба на ПОПГ помеѓу двете групи

ПОПГ	
I Група П	II Група НС
0	4

i.v. Paracetamol + јак опоид	МНОГУ ЈАКА БОЛКА
i.v. Paracetamol + слаб опоид	ЈАКА БОЛКА
i.v. Paracetamol + NSAID i.v. Paracetamol + rescue medicine	УМЕРЕНА БОЛКА
i.v. Paracetamol + rescue medicine	СЛАБА БОЛКА

Мултимодално менаџирање на постоперативна болка

I.V. Paracetamol е атрактивна компонента за мултимодално менаџирање на болка.

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- Значително намалување на болка
- Редукција на дозата на опоидни лекови за - 40% во првите 24 часа
- Намалување на несаканите ефекти поврзани со монотерапија на NSAID и опоидни лекови
- Ублажување на акутна и хронична болка

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Publisher: Department of Anaesthesia and Reanimation Faculty of Medicine
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DELAYED CEREBRAL ISCHEMIA FOLLOWING AN ANEURYSMAL SUBARACHNOID HEMORRHAGE: THE SWORD OF DAMOCLES

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Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is an acute, life-threatening condition that manifests with severe headache (“thunderclap”), loss of consciousness, nausea, and vomiting. It arises as a consequence of a sudden release of blood into the subarachnoid space following a ruptured cerebral aneurysm. In the first 24-72 hours after an ictus, brain damage is the consequence of increased intracranial pressure and transient global ischemia (1). The diagnosis is often made in a prehospital setting and confirmed by a computed tomography (CT) scan or a lumbar puncture. Once the diagnosis is confirmed, the patient is prepared for surgical clipping or endovascular coiling of the ruptured aneurysm.

Obliteration of the aneurysm prevents rebleeding, which is an important risk factor for poor outcome. Is aneurysm obliteration sufficient to ensure a favorable outcome? Although securing the aneurysm prevents rebleeding, extravasated and degraded blood products may contribute to vascular dysfunction, oxidative stress, and neuronal injury, thereby promoting secondary brain injury (2). These reactions lead to the development of delayed cerebral ischemia (DCI), which is one of the main factors of aSAH outcome in patients (3).

Pathophysiology

Following aSAH, blood enters the subarachnoid space, where erythrocytes gradually undergo lysis and release hemoglobin into the cerebrospinal fluid (CSF) (4). Free hemoglobin is initially present primarily as oxyhemoglobin, but it can oxidize to methemoglobin and subsequently release heme (4,5). These hemoglobin degradation products play an important role in the development of cerebral vasospasm (CV) and DCI. Oxyhemoglobin can scavenge nitric oxide (NO), an important vasodilator, thereby contributing to cerebral vasoconstriction and the development of CV (5,6). At the same time, hemoglobin and heme can promote the generation of reactive oxygen species (ROS), leading to oxidative stress and damage to neurons, endothelial cells, lipids, and proteins (4,7).

Heme is subsequently metabolized, primarily through the action of heme oxygenase-1 (HO-1), producing biliverdin, which is further converted to bilirubin, as well as free iron and carbon monoxide. Free iron is particularly important because it can participate in redox reactions that generate highly reactive oxygen species, further enhancing oxidative stress and neuronal injury (8). In addition, heme can activate inflammatory pathways, including microglial and macrophage responses, thereby contributing to neuroinflammation. Bilirubin and its oxidation products may also contribute to oxidative injury and cerebral vasoconstriction (9). Thus, the degradation of erythrocytes and hemoglobin after aSAH results in the accumulation of several biologically active and potentially toxic compounds,

including oxyhemoglobin, methemoglobin, heme, bilirubin, and free iron. Together, these products contribute to oxidative stress, inflammation, endothelial dysfunction, cerebral vasoconstriction, and ultimately secondary brain injury following aSAH and DCI (10).

Clinical presentation of DCI

DCI is one of the most insidious complications of aSAH. DCI is not only a consequence of CV, but also neuroinflammation and endothelial dysfunction (1). DCI is a major complication of aSAH, typically occurring between days 3 and 14 after the initial hemorrhage, typically peaking around 7-10 days (11). However, it may occur later, even several weeks after the initial hemorrhage (12). This persistent threat of secondary brain injury can be regarded as a “sword of Damocles” hanging over the patient, emphasizing the need for continuous monitoring and early detection.

DCI presents as a new focal neurological deterioration that cannot be explained by other causes such as hydrocephalus, seizures, infection, metabolic disturbances, or the effects of sedative medication, or as a decrease of at least 2 points on the Glasgow Coma Scale (GCS), which should last for at least 1 hour and is not apparent immediately after aneurysm occlusion (1). The clinical manifestations depend on the affected vascular territory and may include new focal neurological deficits such as hemiparesis, facial weakness, sensory disturbances, or aphasia. Patients may also develop a decline in the level of consciousness, ranging from mild confusion and disorientation to somnolence, stupor, or coma. Cognitive and behavioral changes, including impaired attention, slowed responses, and altered behavior, may also occur.

Importantly, CV and DCI are not synonymous (13). CV refers to narrowing of the cerebral arteries, usually detected by angiography or suggested by increased blood-flow velocities on transcranial Doppler (TCD), whereas DCI is a clinical syndrome resulting from impaired cerebral perfusion and ischemia. Therefore, significant vasospasm may be present without clinical DCI, while DCI can occasionally occur without prominent angiographic vasospasm.

Risk Factors for DCI

Several factors that increase the risk of DCI have been identified. The most important predictors are the severity of the initial hemorrhage, reflected by a poor neurological grade on admission, and the amount of subarachnoid blood, particularly a high modified Fisher grade (14,15). Intraventricular hemorrhage is also associated with an increased risk of DCI (14). Other potential risk factors for DCI include cerebral vasospasm, hydrocephalus, older age, and systemic disturbances such as hyperglycemia, while early cerebral hypoperfusion and loss of consciousness at ictus have also been investigated as potential predictors (16). Although CV is strongly associated with DCI, DCI can occur even in the absence of significant angiographic vasospasm. Overall, patients presenting with a poor clinical grade, extensive subarachnoid blood, and intraventricular hemorrhage are considered to be at particularly high risk of developing DCI (15,17).

Diagnosis and Assessment of DCI

DCI is associated with poor clinical outcomes and reduced quality of life. Differentiating CV and DCI is essential because CV will not always lead to DCI, and up to 50% of patients with DCI have

no angiographic evidence of vasospasm (13). At first, DCI is diagnosed clinically, but also with TCD, computed tomography angiography (CTA), and computed tomography perfusion (CTP) (11). Digital subtraction angiography (DSA) is the gold-standard imaging modality for visualization of the cerebral vasculature. However, given its invasive nature, it is generally reserved for cases requiring detailed vascular assessment or potential endovascular treatment (18).

When clinically feasible, frequent standardized neurological examinations remain the most important modality for DCI monitoring. New focal neurological deficits, a decline in the level of consciousness, or unexplained neurological deterioration should raise suspicion for DCI (11,19).

The differential diagnosis is particularly important because neurological deterioration after aSAH can result from numerous causes, including rebleeding, hydrocephalus, seizures or non-convulsive status epilepticus, infection, metabolic abnormalities, medication effects, cerebral edema, and intracranial hypertension. Therefore, DCI should generally be considered a diagnosis of exclusion in a patient with new neurological deterioration (19).

In patients with poor-grade aSAH or limited neurological examination, multimodal assessment becomes particularly valuable (11,19). TCD can be used to monitor trends in cerebral blood flow velocities and to identify developing vasospasm. However, increased flow velocity indicates vascular narrowing rather than necessarily clinically significant cerebral ischemia. Consequently, TCD findings should be interpreted in conjunction with the neurological examination and other diagnostic modalities.

CTA can demonstrate large-vessel vasospasm, whereas CTP can provide additional information regarding cerebral blood flow (CBF), cerebral blood volume, mean transit time, and areas of potentially threatened tissue. These techniques may be particularly useful in patients in whom clinical examination is unreliable (19,20).

Continuous electroencephalography (cEEG) monitoring may also contribute to the evaluation of patients with unexplained changes in consciousness by detecting non-convulsive seizures and other patterns associated with cerebral dysfunction (11). Near-infrared spectroscopy (NIRS) is a non-invasive, bedside method for monitoring brain tissue oxygen saturation and an indirect measure of CBF. NIRS has potential for early detection of DCI in patients with poor-grade aSAH (21). Invasive brain tissue oxygenation monitoring (PbO₂) is considered the gold standard for measurement of brain tissue oxygen concentration (22). A level <20mmHg PbO₂ suggests focal cerebral hypoxia, and a level <15 mmHg requires immediate intervention to improve cerebral tissue oxygenation (11). Microdialysis of the brain is an invasive technique for continuous bedside monitoring of extracellular concentrations of lactate, pyruvate, lactate/pyruvate ratio, glutamate, glucose, and glycerol in brain tissue (23). It is used for the detection of ischemia and anaerobic metabolism. The most reliable markers for the prediction of ischemia are glutamate and lactate, as their values peak 24h before clinical ischemia. The microdialysis catheter should be placed in the area at risk for DCI (11).

Biomarkers for DCI Prediction

The development of molecular biology has discovered reliable CSF biomarkers, including micro ribonucleic acid (miRNA), messenger RNA (mRNA), fibrin degradation product (FDP), soluble re-

ceptors, calcium-binding protein (CBP), and high-mobility group box one protein (HMGB1) (11). Serum matrix metalloproteinase-9 (MMP-9), von Willebrand factor (vWF), and vascular endothelial growth factor (VEGF) are increased in patients at risk of DCI (24). Elevated NSE and S100 β levels in CSF and serum have been associated with the development of DCI following aSAH, suggesting their potential utility as predictive biomarkers (25). Cell-free hemoglobin CSF may also serve as a promising biomarker for the prediction of DCI (26).

Prevention of DCI

The risk of DCI is highest during the first two weeks after aSAH. Patients with a greater amount of subarachnoid blood, particularly those with high modified Fisher grades, and patients presenting with poor neurological status are at increased risk (14,15). Management, therefore, consists of prevention, intensive neurological and physiological monitoring, early recognition of cerebral hypoperfusion, and treatment aimed at restoring adequate cerebral perfusion when DCI develops.

Nimodipine

The most important pharmacological intervention for the prevention of DCI is enteral nimodipine (11,19). Nimodipine is a dihydropyridine calcium-channel blocker that has demonstrated a beneficial effect on neurological outcome after aSAH (1). Importantly, its benefit is not adequately explained simply by its effect on angiographic vasospasm, suggesting that neuroprotective and microcirculatory mechanisms may also contribute (27).

The standard regimen is 60 mg administered enterally every 4 hours, generally continued for 21 days after hemorrhage. Hypotension is the principal dose-limiting adverse effect. If systemic hypotension develops, treatment should be individualized, with adjustment of the dosing interval or temporary interruption when necessary rather than exposing the patient to clinically significant hypotension. Current guidelines consider early enteral nimodipine a fundamental component of aSAH management because it reduces the risk of DCI and is associated with improved functional outcomes (19).

It is important to distinguish nimodipine from other calcium-channel blockers. Other calcium-channel blockers have not demonstrated comparable evidence for improving functional outcomes and should not be considered equivalent substitutes (11).

Intrathecal administration of nimodipine and nicardipine has been investigated in several studies. Sustained-release formulations delivered via implants placed at the time of aneurysm clipping have shown promising results (28,29). Intravenous milrinone, a phosphodiesterase-3 inhibitor, was effective in the treatment of DCI (more than two-thirds of cases), but hypotension and tachycardia are side effects of its use (30). As the volume of subarachnoid blood clot is a predictor of DCI, instilling tissue plasmin activator (tPA)/urokinase into the cisterns and ventricles showed a risk reduction of significant DCI (31). Thrombolytics can be instilled into the ventricular or lumbar CSF drainage system.

Maintenance of Euvolemia

Optimization of intravascular volume is another central component of DCI prevention (11). Hypovolemia should be actively avoided because a reduction in circulating volume may compromise cerebral perfusion in the setting of impaired autoregulation. However, prophylactic hypervolemia is not rec-

ommended (19). The historical “triple-H” strategy - hypertension, hypervolemia, and hemodilution - has largely been abandoned because routine hypervolemia does not provide a proven neurological benefit and may cause substantial systemic complications, including pulmonary edema, cardiac strain, electrolyte abnormalities, and increased need for mechanical ventilation (11,19). Crystalloids, such as normal saline (0.9% NaCl), are commonly used for initial volume replacement. Hypertonic saline (3% NaCl) is considered for the reduction of cerebral edema and symptomatic hyponatremia. The use of colloids is controversial due to concerns about increased risk of cerebral edema (11,19).

Current management instead emphasizes goal-directed euvolemia, usually achieved with isotonic crystalloid solutions and individualized assessment of fluid balance, urine output, hemodynamic parameters, and, when appropriate, dynamic measures of fluid responsiveness.

Treatment of Symptomatic DCI

When DCI is suspected or diagnosed, the first step is to identify and correct potentially reversible systemic factors that can worsen cerebral perfusion. These include hypovolemia, hypotension, hypoxemia, anemia, fever, hyperglycemia or hypoglycemia, electrolyte abnormalities, and increased intracranial pressure (19). Once the ruptured aneurysm has been definitively secured by surgical clipping or endovascular treatment, hemodynamic augmentation with induced hypertension can be considered in patients with symptomatic DCI (11).

Induced Hypertension

The physiological rationale for induced hypertension is to increase cerebral perfusion pressure (CPP) and CBF in regions where autoregulation is impaired and distal resistance is increased due to vasoconstriction or microvascular dysfunction (32). Generally, higher mean arterial pressure (MAP) targets during DCI are 80-100mmHg or even higher in some cases (11). Continuous monitoring of CPP can help guide blood pressure management (33).

Vasopressor therapy, most commonly with norepinephrine, may be used to increase mean arterial pressure in a controlled manner (11). The response should be assessed primarily through neurological improvement and, when available, through multimodal measures of cerebral perfusion and oxygenation (22,23).

Importantly, induced hypertension should be considered a treatment for symptomatic DCI rather than a prophylactic intervention. Routine prophylactic elevation of blood pressure in clinically stable patients has not demonstrated sufficient benefit and may expose patients to complications such as myocardial ischemia, arrhythmias, pulmonary edema, and other forms of end-organ injury (19). The blood-pressure target should therefore be individualized rather than universally defined. A reasonable clinical approach is to increase blood pressure progressively while monitoring the patient’s neurological response, cardiac function, intracranial pressure, and systemic tolerance (33). In patients with a secured aneurysm, this strategy may improve perfusion to ischemic yet viable cerebral tissue.

Endovascular Treatment

Patients with severe neurological deterioration attributable to cerebral vasospasm who fail to respond adequately to medical management may require endovascular rescue therapy (33). This approach

should generally be considered in specialized neurointerventional centers. Two principal endovascular strategies are used: balloon angioplasty and intra-arterial vasodilator therapy.

-Balloon Angioplasty

Balloon angioplasty is particularly effective for severe focal vasospasm involving accessible proximal intracranial arteries (34). Mechanical dilation of the constricted arterial segment can produce rapid and substantial improvement in vessel caliber and cerebral blood flow.

Its major limitation is anatomical: distal and diffuse vasospasm may not be amenable to balloon treatment. In addition, angioplasty carries procedure-related risks, including arterial dissection, perforation, thromboembolism, and vessel rupture. Consequently, it is generally reserved for severe vasospasm in appropriately selected patients (11,34).

-Intra-arterial Vasodilators

Intra-arterial administration of vasodilating agents can be used when vasospasm is diffuse, distal, or not suitable for balloon angioplasty (19,34). Agents such as intra-arterial nimodipine, verapamil, and milrinone can produce transient relaxation of cerebral arterial smooth muscle and improve angiographic cerebral blood flow (11). A major limitation is that the effect may be temporary, requiring repeated treatment. Systemic hypotension can also occur, particularly with some vasodilating agents. Monitoring treatment response involves neurological examination and imaging studies (TCD, CTA, CTP, DSA) (11,19,35).

Endovascular therapy should therefore be viewed as a rescue treatment for severe or refractory DCI, rather than a routine prophylactic intervention (19,33).

Therapeutic Options with Limited Evidence

A number of therapeutic strategies have been investigated for the prevention or treatment of DCI, but current evidence does not support their routine use.

Statins have demonstrated biological effects that could theoretically be beneficial in vasospasm and endothelial dysfunction; however, routine statin initiation solely for the prevention of DCI is not currently recommended (19).

Similarly, intravenous magnesium supplementation has not demonstrated sufficient improvement in neurological outcome to support routine use as a DCI-prevention strategy (36). Magnesium should nevertheless be corrected when clinically significant hypomagnesemia is present (37).

Clazosentan, papaverine, fasudil, nitric oxide analogues, erythropoietin, sildenafil, and free radical scavengers (nicaraven) are promising therapeutic agents, but further studies are needed to establish their efficacy in DCI treatment (11,34).

Practical Therapeutic Algorithm Proposal

In clinical practice, management of DCI can be conceptualized as a stepwise approach (19,33):

Prevent DCI: administer enteral nimodipine and maintain euvolemia.

- Monitor closely: perform frequent neurological examinations and use TCD, CTA/CTP, cEEG, or other neuromonitoring techniques when clinically indicated.
- Investigate neurological deterioration: exclude rebleeding, hydrocephalus, seizures, infection, metabolic disturbances, hypoxemia, hypotension, and other causes.
- Confirm or strongly suspect DCI: assess cerebral perfusion and the presence of vasospasm using appropriate imaging and physiological monitoring.
- Optimize systemic physiology: correct hypovolemia, hypotension, hypoxemia, fever, electrolyte disturbances, and elevated intracranial pressure.
- Treat symptomatic DCI: after aneurysm securement, consider controlled induced hypertension with vasopressor support.
- Escalate therapy: in severe or refractory cases, consider endovascular balloon angioplasty and/or intra-arterial vasodilator therapy.
- Continue multimodal assessment: evaluate the neurological and physiological response and modify treatment according to the patient's clinical course.

Conclusion

The contemporary management of DCI following aSAH recognizes cerebral ischemia as a multifactorial dynamic process rather than simply a consequence of angiographic vasospasm. Even after aneurysm securing, the brain remains vulnerable to sudden deterioration. Prevention therefore relies on early enteral nimodipine, maintenance of euvolemia, and intensive neurological surveillance, supported by TCD, CTA, CTP, cEEG, and other neuromonitoring modalities when clinical assessment is limited.

Once symptomatic DCI develops, reversible systemic factors should be corrected and, in appropriately selected patients, induced hypertension may augment cerebral perfusion. Severe or refractory vasospasm may require endovascular rescue therapy. Ultimately, management has shifted from prophylactic hypervolemia toward an individualized, physiology-driven strategy focused on preserving viable brain tissue. The critical challenge remains recognizing the narrow window between reversible ischemia and irreversible infarction, when timely intervention may determine the outcome.

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CLINICAL DATA READINESS IN INFECTION-RELATED SURGICAL ICU ADMISSIONS: A RETROSPECTIVE EVALUATION OF ROUTINE DOCUMENTATION RETRIEVABILITY

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Abstract

Background: We evaluated the completeness and retrievability of core clinical and laboratory treatment, and outcome variables from routine records of infection-related surgical ICU admissions and explored documentation gaps relevant to clinical evaluation and secondary data use.

Material and Methods: We performed a retrospective, single-center, record-based evaluation of infection-related ICU admissions during 2025. The predefined data sources comprised the ICU paper record, admission documentation, clinical progress notes, and laboratory reports physically available in the reviewed patient file. Variables were grouped into bedside physiological/neurological data, laboratory data, organ-support and treatment data, and administrative/outcome data. As an exploratory functional assessment, we evaluated whether the retrieved variables enabled complete retrospective reconstruction of qSOFA, conventional SOFA, NEWS, and MEWS, and conducted a respiratory-rate-based feasibility assessment of SIRS.

Results: Among 196 included patients, supplemental oxygen status, heart rate, systolic blood pressure, and SpO₂ were retrievable in 98.5%, 98.0%, 95.9%, and 93.9% of records, respectively. WBC and platelet count were each retrievable in 77.0%, creatinine in 76.5%, temperature in 67.9%, lactate in 52.6%, and an interpretable mental-status assessment in 52.0% of records. Bilirubin was retrievable in 18.4%, while the numerical respiratory rate was not retrievable within the predefined sources and assessment window. PaO₂ values were documented in arterial blood gas reports, but the corresponding FiO₂ was not routinely recorded in the reviewed paper documentation, preventing paired retrospective derivation of PaO₂/FiO₂.

Conclusions: Routine records of infection-related surgical ICU admissions contained substantial clinically relevant information, but retrievability varied markedly across documentation domains. The most prominent gaps involved structured bedside variables, particularly numerical respiratory rate and neurological assessment, while some laboratory and microbiological information may have been available outside the predefined paper sources. Improving the integration of existing data sources and standardizing a limited set of bedside fields may enhance ICU data readiness while reducing redundant documentation.

Keywords: *intensive care unit; clinical documentation; data retrievability; sepsis; medical records.*

Introduction

Routine intensive care generates a large volume of physiological, laboratory, treatment-related, and outcome-related data. The value of these data for bedside assessment, quality evaluation, audit, and secondary research depends on whether clinically important variables are consistently recorded, are readily retrievable from the available documentation, and linked to an appropriate clinical time point. Incomplete or fragmented documentation may therefore limit data use even when the underlying measurement has been performed, or intervention has been delivered (1,2). In this study, clinical data readiness refers to the extent to which routinely generated information is available in a retrievable and sufficiently structured form for standardized retrospective use.

This issue is particularly relevant in infection-related critical illness, where clinical assessment relies on combinations of bedside observations, organ-support data, and laboratory variables. The Sepsis-3 consensus defines sepsis as life-threatening organ dysfunction caused by a dysregulated host response to infection and operationalizes organ dysfunction using the Sequential Organ Failure Assessment (SOFA) score (2,3). Other commonly used systems, including qSOFA, SIRS, the National Early Warning Score (NEWS), and the Modified Early Warning Score (MEWS), similarly depend on sets of routinely measured clinical variables (2-7). Their retrospective use therefore provides a practical test of whether routine documentation is sufficiently complete for standardized secondary assessment.

Missing data should not automatically be interpreted as evidence that a measurement or intervention was not performed. In paper-based and hybrid information environments, clinically relevant information may be distributed across bedside charts, progress notes, laboratory reports, microbiology systems, anesthesia documentation, and electronic hospital platforms. Therefore, the absence of a retrievable value from a predefined documentation source may reflect fragmentation or limited accessibility rather than the absence of the underlying clinical activity (8). Previous studies have identified respiratory rate as one of the less consistently documented vital signs and have also raised concerns about the reliability of recorded values (9,10). Similarly, incomplete availability of individual SOFA data sets may affect retrospective score reconstruction and related secondary analyses (11,12).

The primary aim of this evaluation was to assess the retrievability of core clinical, laboratory, treatment, and outcome variables from routinely available records of infection-related surgical ICU admissions and to identify the main documentation gaps. Second, this report aims to describe the distribution of missing information across documentation domains and, as an exploratory assessment of data usability, to determine whether the available variables permitted complete retrospective reconstruction of qSOFA, conventional SOFA, NEWS, and MEWS, together with an RR-based feasibility assessment of SIRS.

Materials and Methods

Study Design and Setting

This retrospective, single-center observational evaluation was conducted in the surgical intensive care unit (ICU) of the University Clinical Center “Mother Teresa” in Skopje, North Macedonia. The

unit functions as a tertiary referral ICU and admits postoperative and emergency surgical patients, as well as patients transferred from surgical and medical departments or referred from other hospitals. The study included ICU admissions recorded between January and December 2025. The ICU admission logbook was screened to identify admissions associated with suspected or documented infection, sepsis or septic shock, or infection-related critical illness.

Study Population

A detailed record review was conducted for patients when the ICU admission diagnosis indicated an infection-related condition or a clinical presentation in which infection was considered relevant to critical illness. Screening was performed by one investigator using clinical and diagnostic categories defined before detailed record review and based on internationally accepted terminology for sepsis and infection-related critical illness (2,3). Screening diagnoses included sepsis or septic shock, severe infection, bacteremia, pneumonia with respiratory failure, abdominal infection including peritonitis or cholangitis, urogenital infection, meningitis or encephalitis, necrotizing soft-tissue infection, infection-associated shock or organ dysfunction, and fever requiring ICU-level management.

Admissions primarily related to isolated trauma, intoxication, or acute neurological injury or seizures without suspected infection, as well as elective postoperative admissions requiring routine monitoring without suspected infection or physiological deterioration, were excluded. Duplicate entries for eligible admissions were removed, retaining only the first eligible admission, and records unavailable from the hospital archive were excluded from the final analysis.

Documentation Sources and Data Extraction

Data were collected retrospectively by using a structured study database and predefined variable definitions. Primary record screening and data extraction were performed by one investigator under the supervision of a senior mentor. The predefined study source consisted of the ICU paper record, admission documentation, clinical progress notes, and laboratory reports physically available within the reviewed patient file. Laboratory or microbiological data not contained in the predefined source was not additionally retrieved from electronic hospital systems. Accordingly, the study evaluated source-specific retrievability from the reviewed record rather than definitive institutional availability or non-performance of a measurement or intervention.

The reviewed variables were organized into four documentation domains. Bedside physiological and neurological variables included heart rate, respiratory rate, systolic blood pressure, peripheral oxygen saturation (SpO₂), body temperature, supplemental oxygen requirement (presence or absence), and neurological status. Laboratory variables included white blood cell count, platelet count, serum creatinine, bilirubin, and lactate; oxygenation information required for PaO₂/FiO₂ derivation was also assessed. Treatment and organ-support variables included antimicrobial therapy, vasopressor therapy, mechanical ventilation, and blood culture results. Mechanical ventilation and vasopressor-use status could be ascertained for all patients in the analyzed cohort. Administrative and outcome variables included age, sex, admission diagnosis, source of ICU admission, and ICU outcome.

A variable was considered retrievable when the numerical value or clinically interpretable categorical information required for analysis could be identified in the predefined documentation source. Variables that could not be identified were classified as not retrievable. Clinically non-assessable data,

such as neurological status in patients who were already intubated and/or sedated, were distinguished from undocumented data whenever the record allowed this distinction.

Scope of Paper and Electronic Documentation

The present analysis was intentionally based on the predefined patient record described above. Electronic platforms used in routine care, including “Moj Termin” (electronic database) and separate laboratory or microbiology systems, were not queried to recover additional patient-level values that were absent from the reviewed file. Their potential complementary role is therefore considered in the interpretation of the findings, but patient-level completeness in those systems was not quantified and no combined paper-plus-electronic completeness estimate was generated.

Table 1. Documentation sources and scope of the present evaluation

Documentation source	Used for patient-level extraction	Role in this study
ICU paper record, admission documentation, progress notes	Yes	Primary source for bedside clinical findings, organ-support information, treatment documentation, and narrative assessments.
Laboratory reports physically present in the reviewed patient file	Yes	Source for laboratory values when included in the predefined record.
Electronic hospital, laboratory, and microbiology systems	No	Not queried for recovery of additional patient-level clinical values; complementary electronic completeness was not quantified.

Assessment Window

For physiological and laboratory variables, the measurement closest to the recorded ICU admission time within a predefined window of six hours before or after admission was used. The ICU admission time used for this analysis was retrieved from routine ICU admission documentation and patient charts. The same timestamp is routinely captured in the institutional electronic system (“Moj termin”), which was not used to recover missing clinical values. The same assessment window was applied consistently when evaluating variable availability. Because of the retrospective design, measurements within this interval could have preceded or followed diagnostic, operative, resuscitative, antimicrobial, ventilatory, or vasopressor interventions performed around the time of ICU admission.

Exploratory Reconstruction of Composite Assessment Systems

As a secondary functional assessment of data usability, we evaluated whether qSOFA, conventional SOFA, NEWS, and MEWS could be completely reconstructed based on the variables required by the published frameworks (3-6). We also conducted an exploratory SIRS feasibility assessment. For SIRS, temperature, heart rate, respiratory rate information, and white blood cell count were assessed. Since PaCO₂ was not used as an alternative respiratory criterion in the predefined analysis, this represents RR-based ability to reconstruct rather the respiratory criterion, rather than full reconstruction of all alternative SIRS criteria. qSOFA required respiratory rate, systolic blood pressure, and mental status. Conventional SOFA required complete data across the respiratory, cardiovascular, neurological, coagulation, hepatic, and renal domains; paired PaO₂/FiO₂ data were required for the respiratory

domain. NEWS and MEWS required their standard combinations of respiratory, cardiovascular, temperature, oxygenation, and consciousness variables (3-6).

A composite system was considered completely reconstructable only when all required components were retrievable within the predefined assessment window. Missing values were not imputed, unavailable components were not assumed to be normal, and partial scores were not used as substitutes for complete scores. For the RR-based SIRS feasibility assessment, the respiratory component was considered available only when a numerical respiratory rate could be retrieved. This exploratory analysis was intended to assess the feasibility of retrospective reconstruction based on the available documentation rather than prognostic performance.

Selected early management variables were analyzed descriptively based on the data we could retrieve from the reviewed records. Antimicrobial therapy was classified as therapeutic or prophylactic when the indication could be determined. Time to first therapeutic antimicrobial administration was evaluated only when the recorded data allowed a sufficiently interpretable time interval to be established. Lactate assessment was evaluated separately from the retrieved numerical lactate concentration. Blood-culture data were considered retrievable when evidence of sampling and/or microbiological results was available within the reviewed source; these data were not used to estimate the overall institutional blood-culture acquisition.

Study Outcomes

The primary aim was to assess the retrievability of individual core clinical, neurological, laboratory, treatment, organ-support, and outcome variables and to identify domains with the greatest documentation gaps. Secondary outcomes included the availability of selected early management variables. The complete reconstructability of qSOFA, conventional SOFA, NEWS, and MEWS, together with RR-based SIRS feasibility, was treated as an exploratory functional outcome of documentation completeness.

Statistical Analysis

The analysis was primarily descriptive. Categorical variables were summarized as numbers and percentages. Continuous variables were summarized as mean with standard deviation or median with interquartile range, depending on their distribution. For variables with incomplete availability, the number of patients with retrievable information was reported explicitly. The proportion of retrievable values was calculated for each variable using the full analytic cohort as the denominator unless otherwise specified. Missing variables and variables considered clinically non-assessable were described separately when appropriate. No imputation of missing data was performed.

Results

A total of 694 ICU admissions were recorded during 2025. Screening identified 217 potentially infection-related admissions. Ten duplicate eligible admissions were removed, leaving 207 unique admissions eligible for detailed review. Eleven records could not be retrieved from the hospital archive, leaving a final analytic cohort of 196 patients (Figure 1). The cohort included all principal surgical ICU admission pathways and had substantial requirements for invasive organ support.

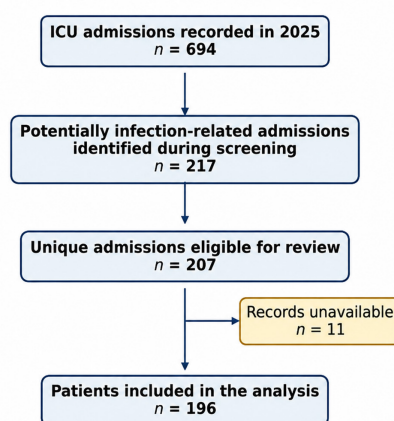


Figure 1. Flow of ICU admissions through screening, eligibility assessment, record retrieval, and final analysis. Ten duplicate eligible admissions were removed between initial screening and the set of unique admissions eligible for detailed review.

Among the 155 patients with retrievable age data, the median age was 69 years (IQR 59-74); 54.1% of the cohort were male. The most common admission sources were the operating room (35.7%) and surgical wards (29.1%). Mechanical ventilation and vasopressor-use status were ascertainable in all 196 patients; 156/196 (79.6%) received mechanical ventilation, and 113/196 (57.7%) received vasopressor therapy. ICU outcome was evaluable in 185 patients, with a mortality rate of 64.9%. Therapeutic antimicrobial therapy was identifiable in 123/196 (62.8%), prophylactic use in 65/196 (33.2%), and no antimicrobial use in 6/196 (3.1%). Among patients receiving therapeutic antimicrobials, administration within one hour was documented in 63/123 (51.2%). Timing was missing or uninterpretable in 20/123 patients, leaving 103 with interpretable timing; among these, 63/103 (61.2%) had documented administration within one hour. Lactate measurement was documented in 149/196 (76.0%), although a numerical lactate value was retrievable in 103/196 (52.6%). Blood-culture data was identifiable in 16/196 (8.2%) within the predefined study source (Table 2).

Table 2. Cohort characteristics and selected early management variables

Variable	Category	n/N	% or summary
Panel A. Cohort characteristics			
Age, years	Median (IQR)	155/196	69 (59-74)
Sex	Male/Female	106/90	54.1% / 45.9%
Admission source	Operating room	70/196	35.7%
	Surgical ward	57/196	29.1%
	Internal medicine departments	42/196	21.4%
	Emergency department	16/196	8.2%
	Other hospital	11/196	5.6%
Mechanical ventilation	Yes	156/196	79.6%
Vasopressor therapy	Yes	113/196	57.7%
ICU mortality	Among evaluable outcomes	120/185	64.9%

Variable	Category	n/N	% or summary
Panel B. Selected early management variables			
Antimicrobial therapy	Therapeutic	123/196	62.8%
	Prophylactic	65/196	33.2%
	None	6/196	3.1%
	Unclassifiable/missing	2/196	1.0%
Therapeutic antimicrobial timing	≤1 h (all therapeutic)	63/123	51.2%
Lactate measurement	Documented as performed	149/196	76.0%
Numerical lactate value	Retrievalable	103/196	52.6%
Blood-culture data	Any retrievalable evidence	16/196	8.2%

Data are n (%) unless otherwise specified. Age was retrievalable for 155/196 patients. Mechanical-ventilation and vasopressor-use status were ascertainable for all 196 patients. ICU outcome was unavailable for 11 patients; mortality was therefore calculated among 185 evaluable outcomes. Therapeutic antimicrobial timing was missing or uninterpretable in 20/123 patients; among the 103 patients with interpretable timing, 63 (61.2%) had documented administration within 1 hour. IQR, interquartile range; ICU, intensive care unit.

Retrievalability was high for cardiovascular and oxygen-related bedside variables. Supplemental oxygen status was identifiable in 193/196 records (98.5%), heart rate in 192/196 (98.0%), systolic blood pressure in 188/196 (95.9%), and SpO₂ in 184/196 (93.9%). Common laboratory variables showed moderate retrievalability: WBC and platelet count were each retrievalable in 151/196 (77.0%), and creatinine in 150/196 (76.5%). Temperature was retrievalable in 133/196 (67.9%).

The largest gaps were concentrated in a smaller set of variables. A numerical lactate value was retrievalable in 103/196 (52.6%) and an interpretable mental-status assessment in 102/196 (52.0%). Bilirubin was retrievalable in 36/196 (18.4%). No numerical respiratory-rate value was available within the predefined source and assessment window; 21 records contained the qualitative term “tachydyspnoic” and seven contained “dyspnoic,” but these descriptions were not converted into numerical values. PaO₂ values were documented in arterial blood-gas reports, but corresponding FiO₂ was not routinely recorded in the reviewed paper documentation. Consequently, paired PaO₂ and FiO₂ information sufficient to derive PaO₂/FiO₂ was not retrievalable within the predefined source and assessment window. Figure 2 and Table 3 summarize the variable-level pattern.

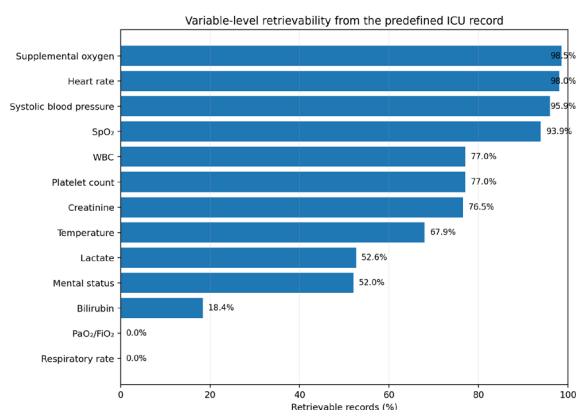


Figure 2. Variable-level retrievalability from the predefined study source. The figure illustrates high re-

trievability for cardiovascular and oxygen-related observations, intermediate retrievability for several laboratory variables, and concentrated gaps in selected bedside and oxygenation variables.

Table 3. Completeness and retrievability of core ICU documentation variables

Domain	Variable	n/N	%	Main limitation / interpretation
Bedside / oxygen	Supplemental oxygen	193/196	98.5%	Highly retrievable
Bedside / oxygen	Heart rate	192/196	98.0%	Highly retrievable
Bedside / oxygen	Systolic blood pressure	188/196	95.9%	Six NM and two unavailable entries
Bedside / oxygen	SpO ₂	184/196	93.9%	Five NM/unmeasurable and seven unavailable entries
Laboratory	WBC	151/196	77.0%	Moderately complete
Laboratory	Platelet count	151/196	77.0%	Moderately complete
Laboratory	Creatinine	150/196	76.5%	Moderately complete
Bedside	Temperature	133/196	67.9%	Incomplete in approximately one third
Laboratory	Lactate	103/196	52.6%	Numerical value less often retrievable than documentation that measurement was performed
Neurological	Mental status	102/196	52.0%	15 explicit unavailable/N/A; 79 blank
Laboratory	Bilirubin	36/196	18.4%	Low retrievability from predefined record
Oxygenation	PaO ₂ /FiO ₂	0/196	0.0%	PaO ₂ was documented in arterial blood-gas reports, but corresponding FiO ₂ was not routinely recorded in the reviewed paper documentation; paired data were unavailable for retrospective derivation.
Bedside	Respiratory rate	0/196	0.0%	21 tachydyspnoic and 7 dyspnoic descriptions; no numerical value

Retrievability required a numerical value or clinically interpretable categorical assessment. Descriptive respiratory terms were not converted to numerical values. Missing components were not imputed or assumed normal. N/A, not applicable; NM, not measurable/unmeasurable as recorded.

Under the predefined complete-case rule, the available documentation did not allow a complete retrospective reconstruction of qSOFA, conventional SOFA, NEWS, or MEWS (0/196 for each), and the RR-based SIRS feasibility assessment was likewise incomplete in all 196 patients. This was a downstream consequence of concentrated documentation gaps rather than a finding of generalized data absence: numerical respiratory rate limited the RR-based SIRS assessment, qSOFA, NEWS, and MEWS; incomplete mental-status documentation further affected qSOFA, conventional SOFA, NEWS, and MEWS; and absent PaO₂/FiO₂ information prevented complete conventional SOFA reconstruction.

Discussion

The main finding of this record-based evaluation was that routine documentation for infection-related surgical ICU admissions contained substantial clinically relevant information, but completeness was uneven across documentation domains. Cardiovascular and oxygen-related observations were highly retrievable, and several common laboratory variables were available in approximately three-quarters

of records. In contrast, the largest gaps involved numerical respiratory rate, neurological assessment, bilirubin, lactate concentration, and $\text{PaO}_2/\text{FiO}_2$. This pattern suggests selective and source-specific incompleteness rather than a generalized absence of ICU documentation.

Respiratory rate was the clearest gap in bedside documentation. Although qualitative descriptors such as “tachydyspnoic” or “dyspnoic” were present in some records, no numerical value was retrievable within the predefined source and assessment window. Qualitative descriptions may be clinically meaningful; however, they do not allow a reproducible threshold-based retrospective assessment. Previous studies have similarly identified respiratory rate as one of the less consistently documented vital signs and have raised concerns about the reliability of recorded values (9,10). These findings support structured numerical recording of respiratory rate as a focused documentation improvement.

Neurological assessment represented another important gap in bedside documentation, with an interpretable mental-status assessment available in approximately half of the cohort. In a surgical ICU, neurological assessment may be complicated by intubation, sedation, residual anesthesia, emergency surgery, and pre-existing neurological impairment. A clinically non-assessable state should therefore remain distinguishable from undocumented information. Missing neurological information has also been recognized as a limitation in retrospective SOFA reconstruction (11,12). Standardized documentation incorporating a concise neurological descriptor or validated consciousness scale, together with an option to indicate sedation or non-assessability, could improve both clinical interpretation and secondary data use.

The laboratory findings illustrate a different aspect of retrievability. WBC, platelet count, and creatinine were available in approximately three-quarters of reviewed files, whereas bilirubin and numerical lactate values were less consistently retrievable. Importantly, electronic systems were not searched when the required information was not available in the predefined record. Low paper-record retrievability, therefore, cannot be interpreted as evidence that a test was not performed, consistent with the broader distinction between data availability and completeness for secondary use (8). Similar considerations apply to blood cultures. $\text{PaO}_2/\text{FiO}_2$. PaO_2 values were present in arterial blood gas reports, but the corresponding FiO_2 was not routinely documented in the reviewed paper charts, preventing retrospective pairing. Difficulties related to incomplete respiratory, bilirubin, and neurological components have also been described in retrospective SOFA assessment (11,12).

These findings suggest that improved integration of data already generated in electronic or departmental systems, together with standardized recording of a limited number of bedside variables, may enhance their usability without unnecessarily increasing documentation burden (1,8). Respiratory rate, neurological status, oxygen-delivery information, and clearly linked laboratory results appear particularly relevant. Structured fields may improve completeness, although completeness alone does not guarantee accuracy, as illustrated by previously reported clustering of recorded respiratory rate values (10).

The exploratory composite assessment analysis further illustrates the effect of individual gaps in the documentation. Under the predefined complete-case approach, qSOFA, conventional SOFA, NEWS, and MEWS could not be completely reconstructed, and the RR-based SIRS feasibility assessment was incomplete in all patients. This should not be interpreted as evidence that clinically important data were generally absent or that the assessment systems themselves perform poorly. These sys-

tems depend on combinations of required variables, and a single unavailable component may prevent complete retrospective reconstruction (3–7). In this cohort, absent numerical respiratory rate affected qSOFA, NEWS, MEWS, and the RR-based SIRS assessment, while conventional SOFA additionally depended on respiratory oxygenation data. The importance of missing individual SOFA components in retrospective analyses has also been demonstrated previously (11,12).

The selected early management variables similarly highlight the distinction between clinical activity and documentary retrievability. Antimicrobial use could be classified in almost all records, whereas precise timing was less consistently interpretable. Lactate measurement was documented more frequently than a corresponding numerical value was retrievable, while blood-culture data were rarely identifiable within the predefined source. Current sepsis guidance emphasizes timely antimicrobial treatment, lactate assessment, and microbiological sampling when clinically appropriate (2). These findings, however, reflect documentary retrievability and should not be interpreted as a direct measure of guideline adherence.

This evaluation has several strengths, including variable-level assessment, use of a predefined assessment window, distinction between unavailable and clinically non-assessable information when possible, and avoidance of unsupported imputation. Several limitations should also be acknowledged. This was a retrospective, single-center evaluation, and findings may not be generalizable to settings with different workflows or information systems. Retrievability was intentionally limited to predefined documentation sources, while electronic laboratory, microbiology, anesthesia, and other institutional systems were not queried for additional patient-level values. Eligibility screening and data abstraction were performed by one investigator without a formal inter-rater reliability assessment. The ± 6 -hour window may also have included measurements obtained before or after major clinical interventions. Finally, the evaluation addressed documentation completeness and data usability rather than diagnostic accuracy, prognostic performance, guideline adherence, or quality of care, and the SIRS analysis was limited to RR-based feasibility because PaCO₂ was not used as an alternative respiratory criterion.

Conclusion

Routine records of infection-related surgical ICU admissions contained substantial clinically relevant information, although retrievability varied across documentation domains. The main gaps were concentrated in selected variables, particularly numerical respiratory rate and neurological assessment, while some laboratory and microbiological data may have been available outside the predefined paper record. Better integration of existing data sources, together with standardized documentation of a limited set of bedside variables, could improve the completeness and usability of routine ICU data for clinical evaluation and secondary use.

Declarations

Ethics approval and consent to participate: The study protocol was approved by the Institutional Review Board of the Department of Anesthesiology and Reanimation, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, North Macedonia. The study involved retrospective analysis of routinely collected clinical data and introduced no study-related intervention or modification of patient management. All data were anonymized before analysis and patient identifiers were replaced

with study codes. Confidentiality was maintained throughout data extraction, database preparation, analysis, and reporting.

Availability of data and materials: The data supporting the findings of this evaluation are available from the corresponding author upon reasonable request, subject to institutional and ethical requirements.

Informed consent: Inapplicable.

Conflict of interest: The authors declare that they have no conflict of interest.

Funding: This research received no external funding.

Authors contributions: M.S. contributed to record screening, data collection, database preparation, and manuscript drafting. A.G.B. contributed to the conception and design of the evaluation, supervision, interpretation of the findings, and critical revision of the manuscript. A.L., M.T.N., P.B.M., contributed to the interpretation of the results, reviewed the manuscript, and approved the final version.

Acknowledgements: The authors thank the colleagues and staff of the surgical intensive care unit who contributed to the routine clinical documentation on which this evaluation was based.

Use of Artificial Intelligence (AI) tools: AI was used to assist with language editing. The authors critically reviewed and edited all AI-assisted output and take full responsibility for the scientific content and final version of the manuscript.

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ASSOCIATION OF MATERNAL ANGIOGENIC MARKERS WITH ADVERSE NEONATAL OUTCOMES IN PREGNANCIES WITH ESTIMATED FETAL WEIGHT BELOW THE 10TH PERCENTILE

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Abstract

Objective: To evaluate the association between maternal angiogenic markers and neonatal outcomes in pregnancies with an estimated fetal weight (EFW) below the 10th percentile.

Methods: This prospective study included 95 singleton pregnancies with EFW below the 10th percentile. Maternal serum placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) were measured, and the sFlt-1/PlGF ratio was calculated. Neonatal outcomes included birth weight, respiratory distress syndrome (RDS), neonatal sepsis, intraventricular hemorrhage (IVH), neonatal death, and duration of neonatal intensive care unit (NICU) hospitalization. Associations were assessed using Spearman's rank correlation.

Results: PlGF was positively correlated with birth weight ($\rho = 0.5654$, $p < 0.001$), whereas sFlt-1 ($\rho = -0.4644$, $p < 0.001$) and the sFlt-1/PlGF ratio ($\rho = -0.5693$, $p < 0.001$) were negatively correlated with birth weight. RDS, neonatal sepsis, and IVH were significantly associated with lower PlGF and higher sFlt-1 concentrations and sFlt-1/PlGF ratios. Lower PlGF levels were weakly associated with neonatal mortality ($\rho = -0.2159$, $p = 0.036$), while sFlt-1 and the sFlt-1/PlGF ratio were not. No significant correlations were observed with NICU hospitalization duration.

Conclusion: Maternal angiogenic imbalance was associated with lower birth weight and increased neonatal morbidity in pregnancies with fetal growth below the 10th percentile. Angiogenic biomarkers may complement conventional fetal assessment in identifying pregnancies at increased risk of adverse neonatal outcomes.

Keywords: fetal growth restriction; small for gestational age; PlGF; sFlt-1; sFlt-1/PlGF ratio; neonatal outcomes

Introduction

Fetal growth restriction (FGR) is characterized by impaired fetal growth resulting from the fetus's inability to achieve its genetically determined growth potential during intrauterine life. It is one of the leading causes of perinatal morbidity and mortality and remains a major challenge in contemporary obstetric practice due to its association with stillbirth, neonatal complications, and adverse long-term health outcomes (1,2,3).

The etiology of FGR is multifactorial. The condition most commonly results from placental insufficiency but may also be associated with fetal chromosomal or structural abnormalities, congenital infections, and maternal exposure to harmful substances or underlying maternal diseases (4). Regardless of the underlying cause, impaired placental function is the predominant mechanism responsible for the majority of FGR cases (5).

A fetus is considered small for gestational age (SGA) when its estimated fetal weight (EFW) is below the 10th percentile for gestational age. However, not all small fetuses are growth-restricted. SGA fetuses have an EFW below the 10th percentile with normal fetal and placental Doppler findings and are generally considered constitutionally small. In contrast, fetal growth restriction describes a pathological condition in which fetal growth is impaired and is accompanied by Doppler evidence of placental or fetal circulatory compromise, reflecting placental dysfunction.

Traditionally, SGA fetuses were regarded as constitutionally small and at relatively low risk for adverse outcomes. Increasing evidence, however, indicates that even fetuses with an SGA below the 10th percentile are at a significantly higher risk of perinatal morbidity and mortality than appropriately grown fetuses (6,7). Population-based studies have demonstrated that the lowest risk of perinatal death occurs among fetuses with birth weights between the 70th and 90th percentiles, whereas the risk increases progressively below the 60th percentile (6). Furthermore, large cohort studies have shown a gradual rise in stillbirth rates among fetuses with estimated fetal weight below the 25th percentile, with fetuses below the 10th percentile being at an approximately five-fold higher risk of intrauterine fetal death compared with those with appropriate growth (8,9).

Accurate identification of fetuses at increased risk of adverse perinatal outcomes is essential for optimal pregnancy management. Current assessment strategies combine ultrasound estimation of fetal size, Doppler evaluation of the uteroplacental and fetoplacental circulation, and, increasingly, maternal serum biomarkers that reflect placental function (10,11). These methods aim to distinguish constitutionally small fetuses from those with pathological growth restriction who require closer surveillance and timely delivery.

Currently, there is no effective treatment that can reverse fetal growth restriction once placental insufficiency has developed (10,11). Therefore, the cornerstone of management is careful fetal surveillance and determining the optimal timing of delivery (12). This decision requires balancing the risks of prematurity due to early delivery against the increasing risk of fetal hypoxia, acidosis, and intrauterine fetal death with prolonged pregnancy.

Among the emerging biomarkers of placental dysfunction, placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) have received considerable attention. Maternal serum concentrations of these angiogenic markers, particularly the sFlt-1/PlGF ratio, correlate with the severity of placental insufficiency and the clinical manifestations of placental disease, including preeclampsia and fetal growth restriction (13). Consequently, these biomarkers may provide valuable information for identifying pregnancies at increased risk of adverse neonatal outcomes and for improving risk stratification in fetuses with estimated fetal weight below the 10th percentile.

Materials and Methods

A prospective observational cohort study was conducted at the University Clinic for Gynecology and

Obstetrics, Skopje. The study population consisted of 95 pregnant women carrying a singleton fetus with an ultrasound-estimated fetal weight (EFW) below the 10th percentile for gestational age.

Participants were enrolled according to predefined eligibility criteria. Women were eligible if they were aged ≥ 18 years, had an EFW below the 10th percentile, were at $\geq 24+0$ weeks of gestation at the time of assessment, were available for follow-up through delivery and neonatal outcome assessment, and provided written informed consent for participation. Women were excluded if they had preeclampsia diagnosed before enrollment, a structural fetal anomaly diagnosed either antenatally or after birth, a multiple pregnancy, a confirmed chromosomal or genetic abnormality, or were in the active phase of labor at enrollment. Pregnancies in which the newborn had a birth weight above the 10th percentile were also excluded from the final analysis.

For each participant, clinical information was recorded using a standardized data collection form. Maternal demographic characteristics included age, weight, and height. Obstetric history included the number and the outcomes of previous pregnancies and a history of preeclampsia, eclampsia, HELLP syndrome, or fetal growth restriction in previous pregnancies. Current pregnancy data included the last menstrual period, gestational age, and number of fetuses.

Gestational age was determined by first-trimester ultrasound dating using crown–rump length (CRL) measurements obtained between 8+0 and 13+6 weeks of gestation (14). For women without available first-trimester ultrasound measurements, gestational age was determined using head circumference (HC) measurements obtained between 14+0 and 21+6 weeks of gestation when the discrepancy between menstrual dating and fetal biometric assessment exceeded 10 days (15).

All participants underwent a standardized ultrasound examination for fetal biometric assessment and evaluation of maternal and fetoplacental Doppler blood flow. Examinations were performed transabdominally using a 4–6 MHz probe on Voluson E8, Voluson E10, or Voluson E6 ultrasound systems (GE HealthCare), with compatible software platforms. Fetal biometry comprised measurements of the biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL). All biometric measurements were obtained in accordance with standardized ISUOG recommendations (15). EFW was calculated using the Hadlock formula (16) and expressed as a percentile according to the Hadlock fetal growth reference (17).

Doppler assessment included the pulsatility index (PI) of the umbilical artery (UA), the pulsatility index of the middle cerebral artery (MCA), and the cerebroplacental ratio (CPR), calculated as the MCA PI divided by the UA PI. Doppler measurements were obtained in accordance with the ISUOG recommendations for Doppler assessment in obstetrics (18).

Maternal venous blood samples were collected and processed in the Biochemical Laboratory of the University Clinic for Gynecology and Obstetrics. Maternal serum concentrations of soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF), together with the sFlt-1/PlGF ratio, were determined using a fully automated electrochemiluminescence immunoassay (ECLIA) platform (Cobas e 411).

The timing and mode of delivery were determined based on the clinical condition of the mother and fetus and in accordance with established recommendations for the surveillance and management of

pregnancies complicated by fetal growth restriction. Indications for delivery included significant abnormalities in fetal or placental Doppler parameters, cardiotocographic evidence suggestive of fetal compromise, a positive fetal stress test, a biophysical profile score <4 , and oligohydramnios.

The neonatal outcomes assessed included birth weight, duration of neonatal intensive care unit (NICU) stay, respiratory distress syndrome (RDS), neonatal sepsis, intraventricular hemorrhage (IVH), and neonatal death. RDS was defined as respiratory morbidity requiring respiratory support with supplemental oxygen for at least 4 hours, including cases diagnosed as transient tachypnea of the newborn.

Statistical Analysis

Statistical analysis of the data obtained from the study was performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois), version 25.0. The Shapiro–Wilk W test was used to assess data distribution. Qualitative variables are presented as absolute and relative frequencies. Quantitative variables are presented as mean, minimum and maximum values, standard deviation, median, and interquartile range. Spearman's rank correlation coefficient was used to analyze the correlation between placental angiogenic markers and selected variables. Statistical significance was defined as $p < 0.05$.

Results

A total of 95 pregnant women from the University Clinic for Gynecology and Obstetrics in Skopje were included in the study. All participants were carrying a fetus with an ultrasound-estimated fetal weight below the 10th percentile. Maternal age ranged from 18 to 56 years, with a mean age of 28.9 ± 6.1 years and a median of 28 years (IQR = 7). Body mass index (BMI) ranged from 17.6 to 41 kg/m², with a mean of 28.2 ± 5.4 kg/m² and a median of 27 kg/m² (IQR = 6.6). The cohort was predominantly composed of pregnancies complicated by late-onset fetal growth restriction, accounting for 71 cases (74.74%). More than half of the participants were nulliparous, with 54 (56.84%) being in their first pregnancy. Regarding parity, the most common category was a history of one previous delivery, reported in 32 women (33.68%). A total of 24 participants (25.26%) were smokers. Thromboprophylaxis was administered to 27 women (28.42%), while 9 (9.47%) received aspirin therapy. Regarding comorbidities, 22 participants (23.16%) had a history of hypertension, while diabetes mellitus was reported in 6 (6.32%) participants. A previous pregnancy complicated by preeclampsia was reported in 5 women (5.26%), while 13 (13.68%) had a history of a pregnancy complicated by fetal growth restriction. The median gestational age at the time of assessment was 35.4 weeks (IQR = 5).

Maternal demographic and clinical characteristics of the study population are presented in Table 1.

Table 1. Maternal and Pregnancy Characteristics of the Study Population (n = 95)

Variable	Value
Maternal age, years	
Mean $\pm$ SD (range)	28.9 ± 6.1 (18–56)
Median (Q1–Q3)	28 (25–32)
Body mass index, kg/m ²	
Mean $\pm$ SD (range)	28.2 ± 5.4 (17.6–41)

Variable	Value
Median (Q1–Q3)	27 (25–31.6)
Fetal growth restriction, n (%)	
Early-onset FGR	24 (25.26)
Late-onset FGR	71 (74.74)
Parity, n (%)	
0	54 (56.84)
1	32 (33.68)
2	4 (4.21)
3	5 (5.26)
Smoking, n (%)	24 (25.26)
Aspirin therapy, n (%)	9 (9.47)
Thromboprophylaxis, n (%)	27 (28.42)
Hypertension, n (%)	22 (23.16)
Diabetes mellitus, n (%)	6 (6.32)
Preeclampsia/eclampsia/HELLP syndrome during current pregnancy, n (%)	3 (3.16)
Previous pregnancy complicated by preeclampsia, n (%)	5 (5.26)
Previous pregnancy complicated by FGR, n (%)	13 (13.68)
Gestational age at assessment, weeks	
Median (Q1–Q3)	35.4 (32–37)

Abbreviations: FGR, fetal growth restriction; HELLP, hemolysis, elevated liver enzymes, and low platelet count; Q1, first quartile; Q3, third quartile; SD, standard deviation.

The median values of the analyzed angiogenic markers were as follows: PlGF, 155 pg/mL (IQR = 322); sFlt-1, 3837 pg/mL (IQR = 5386); and the sFlt-1/PlGF ratio, 25.3 (IQR = 107.8). The distribution of angiogenic marker concentrations is presented in Table 2.

Table 2. Maternal Serum Angiogenic Marker Levels in the Study Population (n = 95)

Variable	Median (Q1–Q3)
PlGF, pg/mL	155 (56–378)
sFlt-1, pg/mL	3837 (1902–7288)
sFlt-1/PlGF ratio	25.3 (5.2–113)

Abbreviations: PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1; Q1, first quartile; Q3, third quartile; IQR, interquartile range.

Neonatal birth weight ranged from 600 to 2950 g, with a mean birth weight of 2059.9 ± 592.9 g. The first birth-weight percentile was the most frequent category, observed in 48 neonates (50.53%). The median Apgar score at 5 minutes was 9 (Q1–Q3: 8–9), with 60 neonates (63.16%) having an Apgar score of 9.

The median duration of NICU stay was 31 days (Q1–Q3: 21.5–48). Respiratory distress syndrome

occurred in 21 neonates (22.11%), neonatal sepsis in 14 (14.74%), and intraventricular hemorrhage in 9 (9.47%). Neonatal death occurred in 4 cases (4.21%). An adverse neonatal outcome was recorded in 50 cases (52.63%).

Table 3. Neonatal Morbidity and Outcomes

Variable	Value
NICU stay, days, median (Q1–Q3)	31 (21.5–48)
Respiratory distress syndrome, n (%)	21 (22.11)
Neonatal sepsis, n (%)	14 (14.74)
Intraventricular hemorrhage, n (%)	9 (9.47)
Neonatal death, n (%)	4 (4.21)
Adverse neonatal outcome, n (%)	50 (52.63)

Abbreviations: NICU, neonatal intensive care unit; Q1, first quartile; Q3, third quartile.

The duration of NICU stay was not significantly correlated with PLGF ($\rho = -0.2339$, $p = 0.23$), sFlt-1 ($\rho = 0.1266$, $p = 0.52$), or the sFlt-1/PLGF ratio ($\rho = 0.1871$, $p = 0.34$).

Table 4. Correlation Between Maternal Angiogenic Markers and Duration of Neonatal Intensive Care Unit Hospitalization

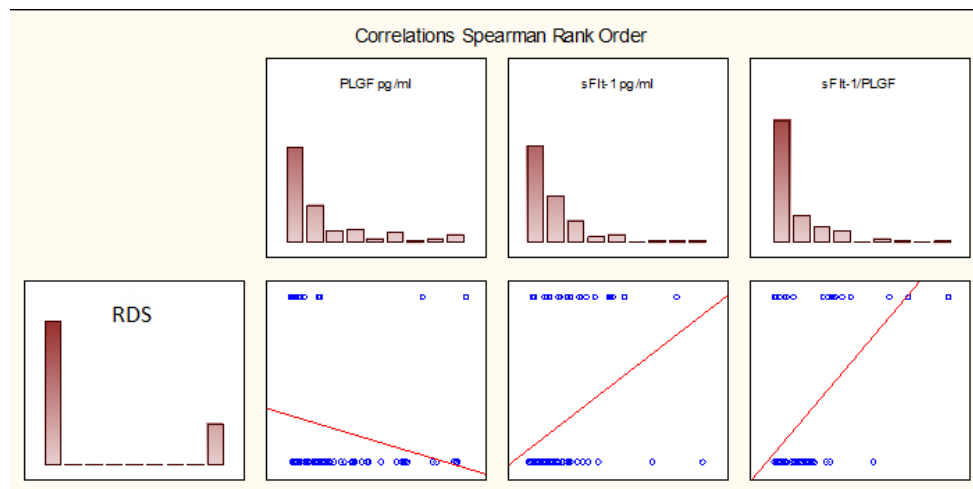
Duration of NICU stay	Spearman ρ	p-value
PLGF (pg/ml)	-0.2339	0.23
sFlt-1 (pg/ml)	0.1266	0.52
sFlt-1/PLGF	0.1871	0.34

Abbreviations: NICU, neonatal intensive care unit; PLGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase-1

Correlation analysis demonstrated a significant moderate negative correlation between respiratory distress syndrome (RDS) and PLGF concentration ($\rho = -0.4007$, $p = 0.0004$). In contrast, RDS was significantly and positively correlated with sFlt-1 concentration ($\rho = 0.3312$, $p = 0.001$) and with the sFlt-1/PLGF ratio ($\rho = 0.4107$, $p < 0.001$).

Table 5. Correlation Between Maternal Angiogenic Markers and Neonatal Respiratory Distress Syndrome

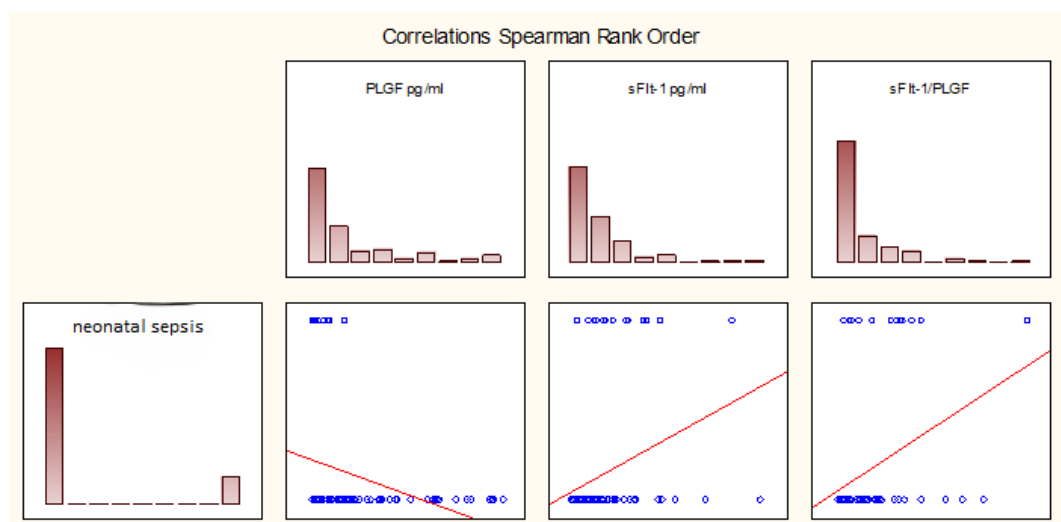
Respiratory distress syndrome &	Spearman ρ	p-value
PLGF (pg/ml)	-0.4070	***0.00004
sFlt-1 (pg/ml)	0.3312	**0.001
sFlt-1/PLGF	0.4107	***0.000036

Figure 1. Correlation Between Maternal Angiogenic Markers and Neonatal Respiratory Distress Syndrome

Correlation analysis demonstrated a significant moderate negative correlation between neonatal sepsis and PLGF concentration ($\rho = -0.3677$, $p < 0.001$). In contrast, neonatal sepsis was significantly and positively correlated with sFlt-1 concentration ($\rho = 0.3303$, $p = 0.001$) and with the sFlt-1/PLGF ratio ($\rho = 0.3769$, $p < 0.001$).

Table 6. Correlation Between Maternal Angiogenic Markers and Neonatal Sepsis

Neonatal sepsis &	Spearman ρ	p-value
PLGF (pg/ml)	-0.3677	***0.00025
sFlt-1 (pg/ml)	0.3303	**0.001
sFlt-1/PLGF	0.3769	***0.00017

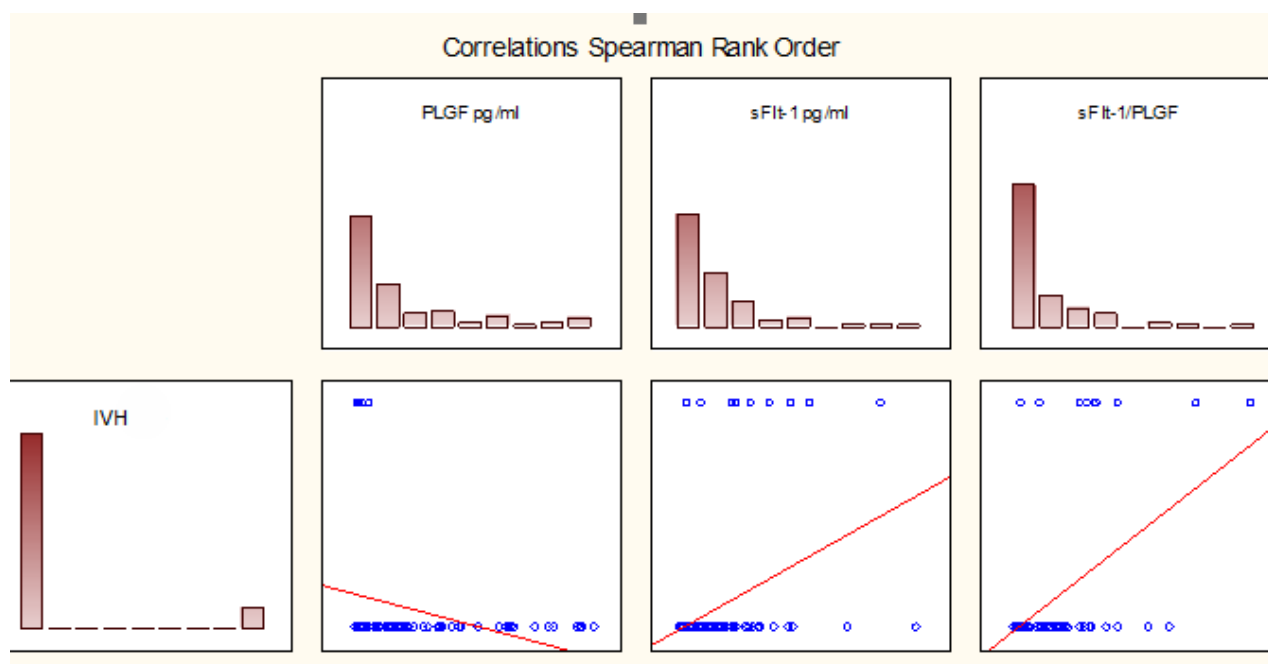
Figure 2. Correlation Between Maternal Angiogenic Markers and Neonatal Sepsis

Spearman correlation analysis demonstrated a significant moderate negative correlation between intraventricular hemorrhage (IVH) and PLGF concentration ($\rho = -0.3932$, $p < 0.001$). In contrast, IVH was significantly and positively correlated with sFlt-1 concentration ($\rho = 0.2870$, $p = 0.0048$) and with the sFlt-1/PLGF ratio ($\rho = 0.3723$, $p < 0.001$).

Table 7. Correlation Between Maternal Angiogenic Markers and Neonatal Intraventricular Hemorrhage

Fetal intraventricular hemorrhage &	Spearman ρ	p-value
PLGF (pg/ml)	-0.3932	0.00008
sFlt-1 (pg/ml)	0.2870	0.0048
sFlt-1/PLGF	0.3723	0.0002

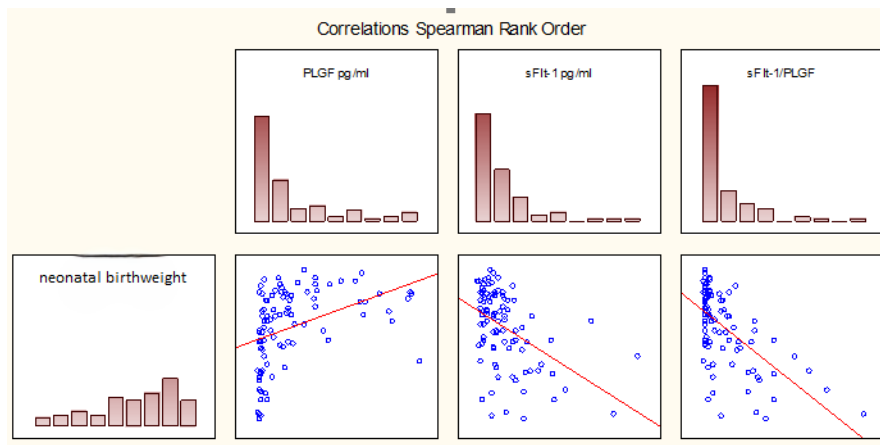
Figure 3. Correlation Between Maternal Angiogenic Markers and Neonatal Intraventricular Hemorrhage



Spearman correlation analysis demonstrated a significant moderate positive correlation between birth weight and PLGF concentration ($\rho = 0.5654$, $p < 0.001$), indicating that higher PLGF concentrations were associated with higher birth weight. In contrast, birth weight was significantly and moderately negatively correlated with sFlt-1 concentration ($\rho = -0.4644$, $p < 0.001$) and with the sFlt-1/PLGF ratio ($\rho = -0.5693$, $p < 0.001$), indicating that higher sFlt-1 concentrations and sFlt-1/PLGF ratios were associated with lower birth weight.

Table 8. Correlation Between Maternal Angiogenic Markers and Neonatal Birth Weight

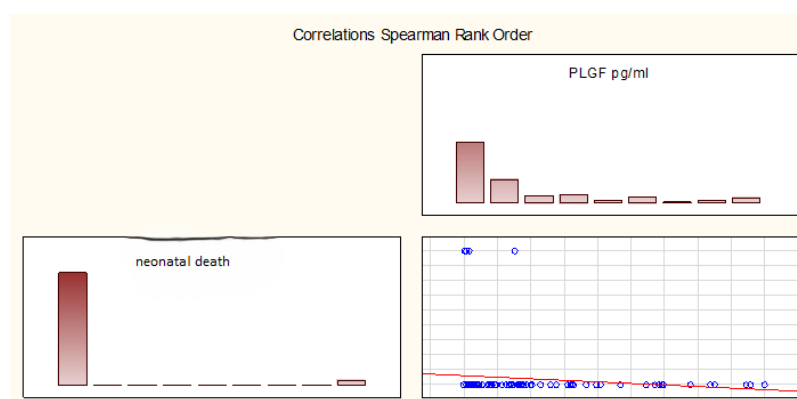
Neonatal birth weight &	Spearman ρ	p-value
PLGF (pg/ml)	0.5654	<0.001
sFlt-1 (pg/ml)	-0.4644	***0.000002
sFlt-1/PLGF	-0.5693	<0.001

Figure 4. Correlation Between Maternal Angiogenic Markers and Neonatal Birth Weight

Spearman correlation analysis demonstrated a significant weak negative correlation between neonatal mortality and PLGF concentration ($\rho = -0.2159$, $p = 0.036$). In contrast, no significant correlations were observed between neonatal mortality and sFlt-1 concentration ($\rho = 0.0937$, $p = 0.37$) or the sFlt-1/PLGF ratio ($\rho = 0.1701$, $p = 0.10$).

Table 9. Correlation Between Maternal Angiogenic Markers and Neonatal Mortality

Neonatal mortality &	Spearman ρ	p-value
PLGF (pg/ml)	-0.2159	*0.036
sFlt-1 (pg/ml)	0.0937	0.37
sFlt-1/PLGF	0.1701	0.1

Figure 5. Correlation Between Maternal Angiogenic Markers and Neonatal Mortality

Discussion

The present study evaluated the association between maternal circulating angiogenic markers and neonatal outcomes in pregnancies complicated by fetal smallness, defined by an estimated fetal weight below the 10th percentile. The principal finding was that an altered maternal angiogenic profile, characterized by lower PlGF concentrations and higher sFlt-1 concentrations and sFlt-1/PlGF ratios, was associated with several indicators of adverse neonatal outcome. These associations were particularly evident for birth weight, respiratory distress syndrome, neonatal sepsis, and intraventricular hemorrhage, whereas the duration of NICU stay was not significantly associated with any of the evaluated angiogenic markers.

The relationship between angiogenic imbalance and neonatal morbidity was evident across several neonatal complications. RDS and neonatal sepsis were negatively associated with PlGF and positively associated with both sFlt-1 and the sFlt-1/PlGF ratio. A similar pattern was observed for IVH, with lower PlGF and higher sFlt-1 and sFlt-1/PlGF ratios associated with this complication. Taken together, these findings suggest that greater angiogenic imbalance is associated not only with impaired fetal growth but also with increased neonatal morbidity.

The findings regarding neonatal mortality were less consistent. Lower PlGF was weakly but significantly associated with neonatal mortality ($\rho = -0.2159$, $p = 0.036$), whereas no statistically significant correlations were found for sFlt-1 or the sFlt-1/PlGF ratio. Given that only four neonatal deaths occurred in the study population, this finding should be interpreted with particular caution. The small number of events limits statistical power and results in considerable uncertainty regarding the strength and stability of the observed associations.

In contrast to the associations with specific neonatal morbidities, none of the angiogenic markers was significantly correlated with the duration of NICU stay. NICU length of stay is a multifactorial outcome influenced by gestational age, birth weight, respiratory support, infection, feeding difficulties, and other clinical factors. Therefore, it may be less directly related to the degree of placental angiogenic imbalance than to individual neonatal complications.

A particularly relevant finding was the association between angiogenic markers and neonatal birth weight. Birth weight showed a moderate positive correlation with maternal PlGF concentration ($\rho = 0.5654$, $p < 0.001$), whereas significant moderate negative correlations were observed with sFlt-1 ($\rho = -0.4644$, $p < 0.001$) and the sFlt-1/PlGF ratio ($\rho = -0.5693$, $p < 0.001$). Our finding of a significant negative association between the sFlt-1/PlGF ratio and neonatal birth weight is consistent with previous studies. Kwiatkowski et al. reported a significant negative correlation between the sFlt-1/PlGF ratio and neonatal birth weight across their entire study population ($R = -0.46$, $p < 0.001$). (19) Similarly, Konopka et al. demonstrated a significant negative correlation between the pre-delivery sFlt-1/PlGF ratio and birth-weight centile for gestational age in pregnancies with isolated fetal growth restriction (iFGR; $R = -0.62$, $p = 0.02$) (20). In our cohort, the sFlt-1/PlGF ratio was also significantly and negatively correlated with neonatal birth weight ($\rho = -0.5693$, $p < 0.001$). These findings support an association between increasing angiogenic imbalance and lower neonatal birth weight, suggesting that the sFlt-1/PlGF ratio may reflect the severity of placental dysfunction and impaired fetal growth.

Our findings are consistent with those of Witwicki et al., who reported a higher incidence of respira-

tory disorders, more frequent NICU admission, and longer hospitalization among neonates in the high sFlt-1/PlGF ratio group. Moreover, an sFlt-1/PlGF ratio ≥ 33 predicted a combined adverse neonatal outcome with a sensitivity of 73% and specificity of 82.2%, and remained independently associated with adverse neonatal outcome in multivariable analysis (21). Similarly, in our study, the sFlt-1/PlGF ratio was significantly associated with respiratory distress syndrome ($p = 0.4107$, $p < 0.001$), supporting the association between greater angiogenic imbalance and increased neonatal morbidity. Although Witwicki et al. reported two neonatal deaths in the high-ratio group and none in the low-ratio group, we found no significant correlation between the sFlt-1/PlGF ratio and neonatal mortality ($p = 0.1701$, $p = 0.10$).

The association between angiogenic imbalance and adverse neonatal outcome observed in our study is also supported by Kamphof et al. In a cohort of 440 singleton SGA pregnancies, they found that the sFlt-1/PlGF ratio was significantly associated with composite adverse perinatal outcome (CAPO; $p < 0.001$). Moreover, the sFlt-1/PlGF ratio remained part of the final multivariable prediction model together with estimated fetal weight and the highest umbilicocerebral ratio, achieving an AUC of 0.75 (95% CI, 0.70–0.81) (22). Similarly, our findings demonstrated significant associations between a higher sFlt-1/PlGF ratio and several adverse neonatal outcomes, including respiratory distress syndrome, neonatal sepsis, and intraventricular hemorrhage. These findings further support the potential value of angiogenic markers, particularly the sFlt-1/PlGF ratio, as complementary indicators of neonatal risk in pregnancies complicated by impaired fetal growth.

Hughes et al. investigated the value of angiogenic biomarkers for risk stratification in pregnancies with suspected fetal growth restriction without signs of preeclampsia at recruitment. Positive angiogenic biomarker results, defined as an sFlt-1/PlGF ratio >38 or PlGF <100 pg/mL, were associated with an increased risk of preterm birth and birth weight below the 3rd centile in pregnancies presenting before 32 weeks of gestation, whereas these associations were not observed in pregnancies presenting between 32 and 37 weeks. These findings suggest that angiogenic imbalance may be particularly informative in early-onset FGR (23). This is consistent with our findings showing that lower PlGF concentrations and a higher sFlt-1/PlGF ratio were associated with lower neonatal birth weight and increased neonatal morbidity, further supporting the potential role of angiogenic biomarkers in identifying pregnancies at increased perinatal risk.

Our findings are also consistent with those of Mendoza et al., who demonstrated the value of the sFlt-1/PlGF ratio for risk assessment in early-onset FGR and SGA (24). In their study, the sFlt-1/PlGF ratio was strongly associated with adverse perinatal outcomes, and prediction models incorporating this biomarker generally performed better than models based solely on maternal characteristics and ultrasound findings. Similarly, in our cohort, a higher sFlt-1/PlGF ratio was significantly associated with lower neonatal birth weight and with increased neonatal morbidity, including respiratory distress syndrome, neonatal sepsis, and intraventricular hemorrhage. These findings support the potential value of the sFlt-1/PlGF ratio as an adjunct to conventional ultrasound and Doppler assessment for identifying growth-restricted fetuses at increased risk of adverse perinatal outcome.

Taken together, the present findings suggest that maternal angiogenic markers may provide information about the severity of placental dysfunction and the subsequent risk of adverse neonatal outcomes in pregnancies with fetuses below the 10th percentile. Of the evaluated parameters, the sFlt-1/PlGF ratio showed relatively consistent associations with birth weight, RDS, neonatal sepsis, and IVH.

As the ratio integrates both the antiangiogenic and proangiogenic components of placental dysfunction, it may potentially provide a more comprehensive reflection of angiogenic imbalance than either marker considered separately.

Conclusion

In conclusion, maternal angiogenic imbalance was associated with fetal growth and several important neonatal morbidities in pregnancies with fetuses below the 10th percentile. Lower PlGF concentrations and higher sFlt-1 concentrations and sFlt-1/PlGF ratios were generally associated with less favorable neonatal outcomes, particularly lower birth weight, respiratory distress syndrome, neonatal sepsis, and intraventricular hemorrhage. These findings support further investigation of angiogenic markers as complementary tools for risk stratification in pregnancies complicated by suspected placental dysfunction. Larger prospective studies incorporating multivariable models are needed to determine whether these biomarkers improve prediction of neonatal outcomes beyond established clinical, ultrasound, and Doppler parameters.

Declarations

Ethics approval and consent to participate: The study was approved by the Ethics Committee of the Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia [No. 03-96/12].

Informed consent: Written informed consent was obtained from all participants prior to inclusion in the study.

Conflict of interest: The authors declare no conflict of interest.

Funding: This research received no external funding.

Availability of data and materials: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions: All authors reviewed and approved the final version of the manuscript.

Artificial Intelligence (AI) statement: AI was used for language editing and improvement of the clarity and readability of the manuscript.

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EVALUATION OF EARLY POSTOPERATIVE KIDNEY DYSFUNCTION IN PATIENTS UNDERGOING ELECTIVE OPEN ABDOMINAL AORTIC ANEURYSM REPAIR WITH INTRAOPERATIVE HYPOTENSION AND CONTINUOUS VASOPRESSOR SUPPORT

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Abstract

Background: Development of postoperative kidney dysfunction is one of the most common and serious perioperative complications in patients undergoing open abdominal aortic aneurysm (AAA) repair resulting from several factors. In this context, intraoperative hypotension and the subsequent need for vasopressor support are associated with postoperative kidney dysfunction, although their individual contributions are difficult to distinguish.

Objectives: To evaluate early postoperative renal-function changes in patients who required continuous intraoperative norepinephrine infusion to treat hypotension.

Methods: A prospective observational cohort study included 20 patients undergoing elective open abdominal aortic aneurysm repair. Patients were divided into two groups according to the intraoperative need for continuous norepinephrine infusion. Intraoperative hemodynamic parameters, acid-base status, and postoperative renal function markers were analyzed and compared between the groups.

Results: Patients receiving intraoperative norepinephrine infusion had significantly lower minimum mean arterial pressure values compared with patients without vasopressor support (61.5 vs. 75.75 mmHg, $p < 0.005$). Significantly higher serum creatinine levels (124.5 vs. 79.88 $\mu\text{mol/L}$, $p = 0.03$) and significantly lower 24-hour urine output (1700 vs. 2450 mL, $p = 0.002$) were observed in the norepinephrine group 48 hours following surgery.

Conclusion: Patients requiring intraoperative vasopressor support during open abdominal aneurysm repair experience higher level of hemodynamic instability, more severe hypotension, and less favorable early postoperative kidney dysfunction markers. However, these findings cannot establish direct adverse renal dysfunction effects.

Keywords: *acute kidney dysfunction; abdominal aortic aneurysm; intraoperative hypotension; vasopressor support.*

Introduction

Open surgical repair of an abdominal aortic aneurysm (AAA) is a major vascular procedure associated with significant hemodynamic fluctuations, aortic cross-clamping, potential blood loss, and ischemia-reperfusion injury. These perioperative challenges may compromise renal perfusion and contribute to the development of early postoperative renal dysfunction, ranging from transient alterations in renal function to clinically significant acute kidney injury (AKI) (1,2).

Therefore, postoperative kidney dysfunction is an important concern in these patients. Renal dysfunction after open AAA repair rarely has a single cause. Reduced perfusion pressure, ischemia-reperfusion injury, and perioperative inflammation may interact with patient-related factors such as older age, hypertension, diabetes, and pre-existing renal impairment (2–4). The frequency of postoperative renal dysfunction varies across studies, partly due to differences in case mix and diagnostic criteria (1,2).

Intraoperative hypotension represents an important potentially modifiable factor associated with postoperative renal dysfunction. Observational studies have demonstrated that both the severity and duration of intraoperative hypotension are associated with postoperative kidney dysfunction (5–7). Contemporary perioperative recommendations emphasize maintaining adequate mean arterial pressure (MAP), generally at least 60–65 mmHg, to reduce the risk of hypotension-associated organ injury. Nevertheless, optimal blood pressure targets should be individualized according to baseline cardiovascular status, comorbidities, and clinical condition (8).

To maintain adequate systemic perfusion, vasopressors such as norepinephrine are frequently administered when hypotension persists despite appropriate hemodynamic optimization. Norepinephrine increases systemic vascular resistance and arterial pressure primarily through alpha-adrenergic receptor stimulation. Although norepinephrine may improve systemic and renal perfusion pressure, its relationship with postoperative renal outcomes is complex. Vasopressor requirement may reflect the severity of underlying hemodynamic instability rather than a direct adverse effect of the drug itself (9,10).

Recent observational evidence suggests that both intraoperative hypotension and cumulative norepinephrine dose are associated with postoperative renal dysfunction in patients undergoing noncardiac surgery. However, these findings do not establish a causal relationship between norepinephrine administration and renal injury (10). This distinction is particularly relevant during major vascular surgery, where hemodynamic instability, aortic cross-clamping, and reperfusion may simultaneously affect renal perfusion and contribute to postoperative renal dysfunction or AKI.

Acute kidney injury is a clinically significant form of acute renal dysfunction characterized by a rapid deterioration in kidney function. According to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, AKI is diagnosed when serum creatinine increases by ≥ 0.3 mg/dL (≥ 26.5 μ mol/L) within 48 hours, rises to ≥ 1.5 times baseline within the preceding seven days, or when urine output decreases below 0.5 mL/kg/h for at least six hours (13). These criteria provide a standardized frame-

work for diagnosing and classifying AKI in patients undergoing major surgical procedures.

However, early postoperative deterioration in renal function may occur without meeting the criteria to establish a AKI formal diagnosis. Changes in serum creatinine and urine output may provide clinically relevant information during the early postoperative period, even when formal patient-level KDIGO classification has not been performed.

Early recognition of postoperative renal dysfunction is clinically important, as deterioration in renal function, particularly when progressing to AKI, may be associated with increased morbidity, prolonged hospitalization, higher healthcare costs, and unfavorable long-term renal and cardiovascular outcomes (3,4,12).

Despite increasing recognition of the relationship between intraoperative hypotension, vasopressor administration, and postoperative renal complications, the association between hemodynamic instability, norepinephrine requirement, and early postoperative changes in renal function following open AAA repair warrants further investigation.

Therefore, the present study aimed to evaluate the association between intraoperative hypotension, the requirement for continuous norepinephrine infusion, and early postoperative renal dysfunction in patients undergoing elective open abdominal aortic aneurysm repair. Early postoperative renal function was assessed using serum creatinine levels and urine output within the first 48 hours after surgery, without formal classification of AKI according to KDIGO criteria.

Objective

The primary objective was to compare early postoperative renal function markers in patients who did and did not require continuous intraoperative norepinephrine during elective open infrarenal AAA repair.

The secondary objectives were to describe differences in minimum intraoperative MAP, acid-base parameters, perioperative fluid administration, aortic cross-clamp duration, urine output, and length of hospital stay. The study was exploratory and was not designed to establish causality.

Materials and Methods

This study was conducted as an observational prospective cohort pilot study that included patients undergoing elective surgical treatment for infrarenal abdominal aortic aneurysm repair. The research was conducted over a six-month period at the University Clinic for Anesthesia, Reanimation, and Intensive Care (KARIL) in Skopje, in collaboration with the University Clinic for Thoracic and Vascular Surgery. The study cohort was hospitalized and treated at the University Clinic for Thoracic and Vascular Surgery in Skopje. Prior to enrollment in the study, patients provided written informed consent.

All patients aged 60-80 undergoing infrarenal surgical AAA repair were included in the study, while patients with pre-existing renal disease, emergency cases, patients with confirmed chronic kidney disease, patients with impaired left ventricular systolic function ($EF < 45\%$), patients scheduled for endovascular treatment, and those who did not sign an informed consent form were not included.

To meet the study objectives, enrolled patients were categorized into two groups after surgery based on their need for intraoperative vasopressor support. The first group (n=10) included patients who received continuous vasopressor (norepinephrine) infusion only during the intraoperative period based on MAP (according to the protocol as POQI;2024; Saugel et al.(10)); while the second group (n=10) included patients in whom vasopressor support was not used.

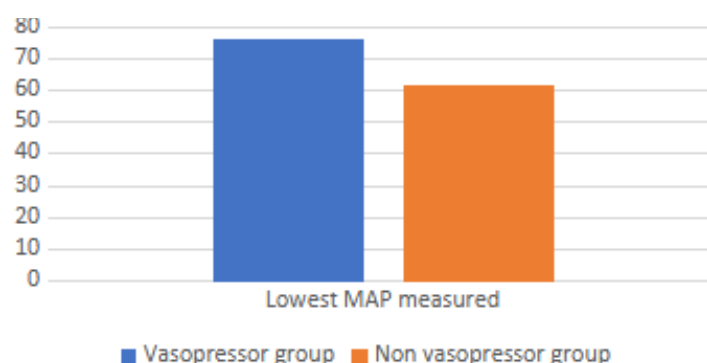
Data obtained from all patients' data sheets were evaluated and analyzed for demographic data, hemodynamic profile, the duration of hypotension, and the intraoperative administration of crystalloids, colloids, blood, and blood products (measured in milliliters). With a focus on the intraoperative period, and postoperative values of generally accepted markers of renal injury were also analyzed, as well as the time for cross-clamping of the aorta, acid-base status, duration of the procedure, and postoperative outcomes. In the postoperative period, 48 hours after the intervention, levels of renal injury markers were analyzed and compared between the two study groups, the cumulative dose of vasopressor use in the first group and the time of vasopressor usage.

Standard descriptive statistical analysis was used in the study to summarize data including mean and median values. Depending on the distribution of numerical values, comparison between the two groups were performed using the Student's t-test or the Mann-Whitney U test, as appropriate.

Results

A total of 20 patients were included in the study, 10 (50%) received a continuous vasopressor (norepinephrine) infusion during the intraoperative period, while the remaining patients did not receive vasopressor support. Gender distribution was not a statistically significant differentiator between the two groups, and most of the patients in both groups were male. The mean age was not statistically different between the two groups (69.13 (SD 6.58) vs 67.63 (SD 7.21) (Student's t-test: $t=0.43$, $p=0.33$).

Group of patients receiving norepinephrine infusion during the intraoperative period, showed statistically significantly lower values of the lowest mean arterial pressure with a mean value of 61.5 mmHg, compared to 75.75 mmHg in patients without intraoperative vasopressor support (Student's t-test: $t=2.97$, $p < 0.005$) (Graph 1). Duration of vasopressor infusion in this group was $56.9 \text{ min} \pm 23.5 \text{ min}$ (mean $\pm$ SD). Patients in this group received a continuous infusion of norepinephrine with mean dose of $0.215 \pm 0.078 \text{ } \mu\text{g/kg/min}$ and cumulative dose of $940.9 \pm 623.7 \text{ } \mu\text{g}$ in total.



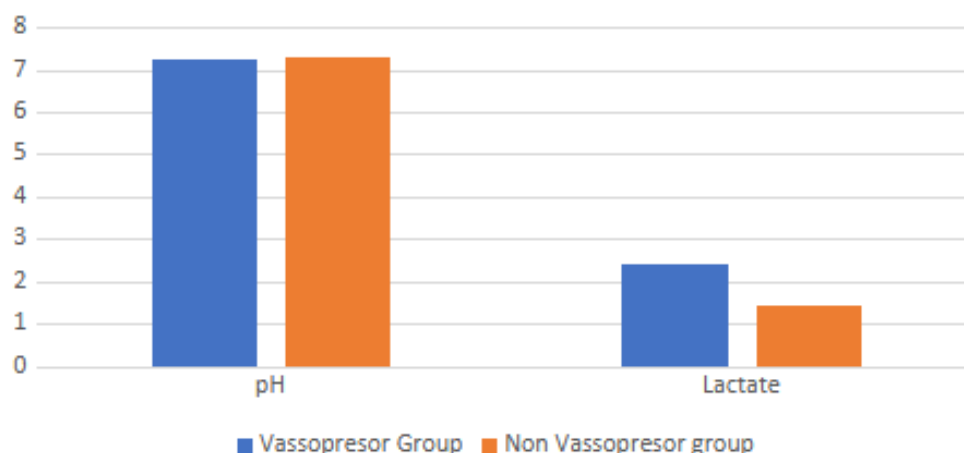
Graph No. 1: Graphical representation of the mean lowest MAP in both study groups.

Table No. 1: Doses of norepinephrine received in the vasopressor group

Variable	Norepinephrine group (n=10)
Norepinephrine dose ($\mu\text{g/kg/min}$)	0.215 ± 0.078
Cumulative norepinephrine dose (μg)	940.9 ± 623.7
Duration of norepinephrine infusion (min)	56.9 ± 23.5

No statistically significant difference regarding intraoperative crystalloid infusion volumes was detected; the mean crystalloid administration was 4,000 mL in the norepinephrine group and 3,500 mL in the no-norepinephrine group ($p=0.23$).

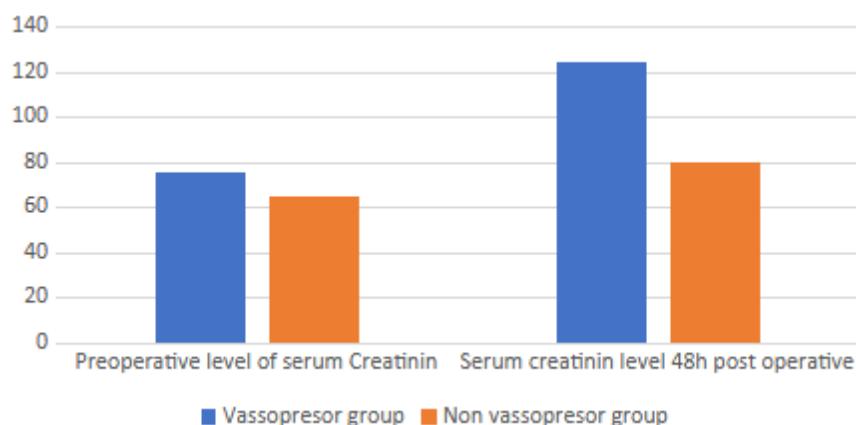
Equal amounts of colloids were infused in both groups during the intraoperative period. Furthermore, no statistically significant differences were observed regarding cross-clamp duration: 77.88 minutes for patients receiving continuous norepinephrine infusion versus 70.25 minutes for those not receiving norepinephrine infusion (Student's t-test: $t=1.14$; $p=0.13$). In the group of patients treated with norepinephrine infusion, non-significantly lower pH values were measured with a median of 7.25 compared to 7.34 in patients treated without vasopressor support (Mann-Whitney U test: $U=21$; $z=-1.1$; $p=0.123$) (Graph 2) along with non-significantly higher lactate levels in patients receiving vasopressor support (median 2.41 vs. 1.43 in those not requiring vasopressors; Mann-Whitney U test: $U=18$; $z=-1.4$; $p=0.07$) (Graph 2).

**Graph No. 2:** Graphical representation of pH and lactate levels in both study groups.

In patients receiving continuous vasopressor support intraoperatively, higher preoperative serum creatinine levels were measured with a median of 75.63 compared to 65.07 in those who did not require continuous norepinephrine infusion (Mann-Whitney U Test: $U=21$; $z=-1.1$, $p=0.123$) (Graph No. 3). The difference was not statistically significant.

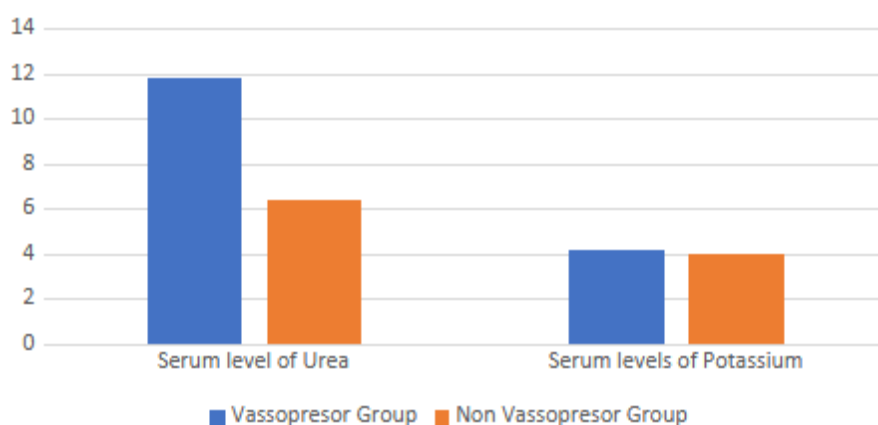
Forty-eight hours after the intervention, statistically significantly higher serum creatinine levels were measured, with a mean value of $124.5 \mu\text{mol/L}$ in patients who received intraoperative norepinephrine infusion, compared to $79.88 \mu\text{mol/L}$ in patients who did not require continuous vasopressor support

(Student's t-test: $t=1.96$; $p=0.03$) (Graph No. 3).



Graph No. 3: Preoperative creatinine level and creatinine level at 48 hours after surgery in patients with and without the need for vasopressor support.

Furthermore, in patients requiring intraoperative vasopressor support, measurements taken 48 hours after the intervention showed, albeit statistically nonsignificant, higher urea levels (mean: 11.83 vs. 6.38 in patients not requiring vasopressors; Student's t-test: $t=1.29$, $p=0.1$; Graph 4) and potassium levels (median: 4.23 vs. 3.99; Mann-Whitney U test: $U=29$, $z=-0.3$, $p=0.37$; Graph 4).



Graph No. 4: Urea and potassium levels 48 hours after the intervention in patients with and without the need for intraoperative vasopressor support.

In patients receiving intraoperative norepinephrine infusion, insignificantly lower urine output values were measured with a median of 500 mL, compared to 700 mL in patients who did not receive a vasopressor (Mann-Whitney U Test: $U=30$; $z=-0.2$; $p=0.41$).

Forty-eight hours after the procedure, patients who had received intraoperative vasopressor support showed statistically significantly lower values for 24-hour urine output (median: 1700 mL), compared to the group that did not receive continuous intraoperative vasopressor support (median: 2450 mL) (Mann-Whitney U Test: $U=5.50$; $z=-2.7$; $p=0.002$). Renal markers are shown in Table 3.

No statistically significant difference was found in relation to the length of hospital stay between the two analyzed groups; the mean duration was 8.5 days for patients receiving vasopressor infusion versus 8 days for those who did not receive a vasopressor intraoperatively (Student's t-test: $t=0.31$; $p=0.37$).

Table No. 2: Perioperative characteristics according to intraoperative norepinephrine requirement

Variable	Norepinephrine (n=10)	No norepinephrine (n=10)	p value
Age, years	69.13 $\pm$ 6.58	67.63 $\pm$ 7.21	0.33
Minimum MAP, mmHg	61.5	75.75	<0.005
Crystalloids, mL	4000	3500	0.23
Aortic cross-clamp duration, min	77.88	70.25	0.13
pH	7.25	7.34	0.123
Lactate, mmol/L	2.41	1.43	0.07
Intraoperative urine output, mL	500	700	0.41

Table No. 3: Renal function markers and postoperative outcome

Variable	Norepinephrine (n=10)	No norepinephrine (n=10)	p value
Baseline serum creatinine, μ mol/L	75.63	65.07	0.123
Serum creatinine at 48 h, μ mol/L	124.5	79.88	0.03
Urea at 48 h	11.83	6.38	0.10
Potassium at 48 h, mmol/L	4.23	3.99	0.37
24-h postoperative urine output, mL	1700	2450	0.002
Length of hospital stay, days	8.5	8.0	0.37

Values are presented as mean $\pm$ SD or as the reported central value from the source dataset, according to the original statistical analysis. MAP, mean arterial pressure.

Discussion

Acute kidney dysfunction is one of the most serious complications following open repair of an abdominal aortic aneurysm. Open repair of an abdominal aortic aneurysm (AAA) is a complex and highly invasive vascular surgical procedure associated with profound systemic physiological stress and significant intraoperative hemodynamic fluctuations. The combination of manipulation of major blood vessels, aortic clamping, potential massive blood loss, and subsequent reperfusion imposes a complex pathophysiological burden on organ systems, particularly the kidneys (1-3).

Among numerous potentially modifiable factors, intraoperative hypotension is considered one of the most important risk factors for postoperative renal dysfunction. Numerous studies have shown that even brief periods of reduced mean arterial pressure are associated with an increased risk of postoperative organ dysfunction, specifically acute kidney injury and complications(5–7). The kidneys are particularly sensitive to changes in systemic perfusion, and prolonged or severe hypotension can lead to impaired renal blood flow, reduced glomerular filtration, and ischemic injury (1,4,7).

The PeriOperative Quality Initiative (POQI) international consensus statement recommends avoiding sustained intraoperative hypotension and generally maintaining MAP at or above 60–65 mmHg, with adjustments based on individual patient needs and clinical conditions (10). In patients undergoing open AAA repair, maintaining adequate perfusion pressure is particularly important because aortic cross-clamping, unclamping, blood loss, and anesthesia-related vasodilation may produce substantial changes in systemic and regional hemodynamics.

In modern anesthetic practice, norepinephrine is the first-choice vasopressor for the treatment of intraoperative arterial hypotension. Its action is mediated primarily through alpha-adrenergic stimulation, resulting in vasoconstriction, increased systemic vascular resistance, and the maintenance of mean arterial pressure. It enables the maintenance of systemic arterial pressure and adequate organ perfusion during hemodynamic instability, particularly in patients undergoing major surgical procedures associated with significant hemodynamic fluctuations. In patients undergoing open repair of an abdominal aortic aneurysm, norepinephrine is frequently used to correct hemodynamic instability caused by aortic clamping and reperfusion phenomena, changes in afterload, blood loss, and anesthesia-induced vasodilation. Consequently, the need for intraoperative norepinephrine infusion can be considered an indirect indicator of a more complicated intraoperative course and more pronounced hemodynamic instability (1,7,10-13).

In the present prospective observational study, patients requiring continuous intraoperative norepinephrine infusion exhibited significantly lower minimum mean arterial pressure (MAP) values, compared with patients who did not receive vasopressor support (61.5 vs. 75.75 mmHg; $p < 0.005$). The mean minimum MAP in the norepinephrine group was below 65 mmHg - a threshold commonly associated with an increased risk of postoperative organ injury. This finding is particularly significant because the average lowest MAP value in this group fell below the 65 mmHg threshold, which is currently considered a critical limit below which the risk of organ hypoperfusion and postoperative acute kidney dysfunction and injury increases substantially. Previous studies by Walsh et al. and Salmasi et al. demonstrated associations between intraoperative hypotension and postoperative renal complications; while the systematic review by Wesselink et al. emphasized the importance of both the severity and duration of hypotensive episodes (5–7).

In our study, patients receiving norepinephrine had significantly lower minimum MAP values, suggesting greater intraoperative hemodynamic instability. Therefore, the observed association between norepinephrine administration and postoperative renal dysfunction should not be interpreted as evidence of a direct effect of norepinephrine. Rather, vasopressor requirement may represent a marker of more pronounced circulatory instability and underlying disturbances in tissue perfusion. This distinction is particularly important because norepinephrine was administered based on clinical need rather than randomized allocation.

Serum creatinine is a routinely used marker for evaluating changes in renal function and is incorporated into the Kidney Disease: Improving Global Outcomes (KDIGO) diagnostic criteria for AKI (13). In the present study, preoperative serum creatinine levels did not differ significantly between the groups. However, 48 hours after surgery, patients requiring intraoperative norepinephrine support exhibited significantly higher serum creatinine concentrations than patients who did not receive vasopressors (124.5 vs. 79.88 $\mu\text{mol/L}$; $p = 0.03$).

These findings indicate an association between intraoperative vasopressor requirement and impaired early postoperative renal function. Nevertheless, the absence of a statistically significant difference in baseline creatinine does not establish equivalence of preoperative renal function, particularly in a small study population. Furthermore, although serum creatinine increased in the norepinephrine group, formal patient-level KDIGO classification was not performed. Consequently, the present findings should be interpreted as changes in early postoperative renal function rather than as a confirmed difference in AKI incidence.

In addition to serum creatinine, urine output represents an important clinical parameter for assessing renal function and is included in the KDIGO diagnostic criteria for AKI (11-14). In our study, intraoperative urine output did not differ significantly between the groups. However, postoperative 24-hour urine output was significantly lower in patients requiring norepinephrine support compared with those who did not receive vasopressors (1700 vs. 2450 mL; $p=0.002$).

The lower postoperative urine output observed in the norepinephrine group, together with higher postoperative serum creatinine concentrations, suggests less favorable early renal functional outcomes in patients experiencing greater intraoperative hemodynamic instability. Nevertheless, total 24-hour urine volume alone is insufficient for diagnosing oliguria according to KDIGO criteria, based on which the urine output is evaluated relative to body weight and duration. Moreover, postoperative urine output may be influenced by fluid balance, diuretic administration, neurohormonal responses, and other perioperative factors. In the present study, no statistically significant differences were observed between the groups in the volume of administered crystalloids and colloids or the duration of aortic cross-clamping. Although these findings reduce the likelihood that the measured differences in these variables alone explain the observed renal outcomes, residual confounding cannot be excluded. The relatively small sample size also limits the ability to identify clinically relevant differences in other perioperative factors.

Additional indicators of tissue perfusion, including arterial pH and serum lactate, were evaluated. Patients requiring norepinephrine support showed numerically lower pH values (7.25 vs. 7.34) and higher serum lactate concentrations (2.41 vs. 1.43 mmol/L). However, these differences did not reach statistical significance. Therefore, they should be interpreted as descriptive findings rather than evidence of a confirmed difference in systemic tissue hypoperfusion. Nevertheless, their direction is compatible with the greater hemodynamic instability observed in patients requiring vasopressor support.

Taken together, our findings suggest that patients requiring continuous intraoperative norepinephrine infusion during elective open AAA repair experience greater hemodynamic instability and less favorable early postoperative renal functional parameters. These observations are consistent with previous studies demonstrating associations between intraoperative hypotension, vasopressor exposure, and postoperative kidney injury (5–7,9,10).

Limitations and Further Suggestions

The present study has several limitations. First, the sample size only 20 patients limited statistical power and the generalizability of the findings. Second, the observational design and clinically determined administration of norepinephrine introduce potential confounding by indication. Third,

although minimum MAP values were recorded, the cumulative duration and severity of hypotension were not quantified in the present analysis. Fourth, renal function was evaluated using serum creatinine and urine output without formal patient-level KDIGO classification, preventing reliable determination of AKI incidence and severity.

Despite these limitations, the study provides preliminary clinical evidence supporting the importance of careful intraoperative hemodynamic monitoring and early postoperative assessment of renal function in patients undergoing open AAA repair.

Conclusion

According to our study, continuous intraoperative norepinephrine requirement was associated with lower minimum MAP values, higher serum creatinine concentrations at 48 hours after surgery, and reduced postoperative urine output following elective open AAA repair. These findings suggest that vasopressor requirement may identify patients at increased risk of early postoperative renal dysfunction. However, the observational design does not allow the establishment of a causal relationship between norepinephrine administration and renal impairment. Larger prospective studies incorporating detailed hypotension exposure, vasopressor dosing, and standardized KDIGO assessment are required to clarify these associations.

Declarations

Ethics approval and consent to participate: This study was approved by the Ethics Committee of the Faculty of Medicine, Ss. Cyril and Methodius University in Skopje (Approval No. 02-2848/15, dated 7 May 2026).

Informed consent: Written informed consent was obtained from all participants prior to inclusion in the study.

Conflict of interest: The authors declare no conflict of interest.

Funding: This research received no external funding.

Availability of data and materials: Data are available from the corresponding author upon reasonable request.

Authors' contributions: All authors reviewed and approved the final version of the manuscript.

Acknowledgements: Not applicable.

Artificial Intelligence (AI) statement: No AI tools were used in the preparation of this manuscript.

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CHANGES IN ASTHMA PREVALENCE, SYMPTOMS, AND ASSOCIATED RISK FACTORS AMONG ADOLESCENTS IN SKOPJE, 2016–2026

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Abstract

Background: Asthma is one of the most common chronic diseases in childhood, with considerable differences in prevalence and trends worldwide.

Objective: To assess asthma prevalence and changes over the 2016–2026 period among adolescents in Skopje, and to examine changes and associations with selected personal, family, behavioral, and environmental factors.

Materials and Methods: Data from two cross-sectional surveys conducted in Skopje in 2016 and 2026 were compared. Both surveys used the same standardized questionnaire on respiratory health and asthma. The analysis included 1,013 adolescents aged 12–15 years (690 in 2016 and 323 in 2026). Statistical analyses were performed using IBM SPSS Statistics version 25.0 and JASP version 0.98.1.

Results: The prevalence of doctor-diagnosed asthma was low (3.4%) and showed a slight increase, although the difference was not statistically significant. In contrast, several asthma-related symptoms increased significantly. Current wheeze increased from 5.5% to 9.9%, exercise-induced wheeze from 1.9% to 6.2%, and dry night cough from 9.6% to 20.7%. Measures of symptom severity also increased significantly. In the fully adjusted models, household dampness, maternal asthma, frequent fast-food consumption, paracetamol use, and truck traffic were positively associated with several asthma-related symptoms.

Conclusion: Asthma and asthma-related symptoms increased over the ten-year period, while underdiagnosis and inadequate treatment remained important concerns. The findings suggest a need for better education for healthcare professionals to improve asthma diagnosis and treatment, together with education of patients and parents on the regular and correct use of prescribed therapy.

Keywords: *asthma; adolescents; risk factors; trends; wheeze.*

Introduction

Asthma is one of the most common chronic diseases in childhood. It results from the interaction between genetic predisposition and environmental factors. It is a heterogeneous disease commonly characterized by chronic airway inflammation and persistent bronchial hyperresponsiveness to different stimuli. Clinically, asthma presents with wheeze, shortness of breath, chest tightness, and/or cough, which may vary in intensity, together with variable expiratory airflow limitation (1).

Large international epidemiological studies, particularly the International Study of Asthma and Allergies in Childhood (ISAAC), have revealed considerable geographical differences in the prevalence of asthma and asthma-related symptoms among adolescents and have enabled comparisons of trends across different populations. Globally, asthma prevalence is higher in economically developed countries, whereas more severe symptoms and underdiagnosis are more common in developing countries (2). Comparison of ISAAC Phase Three with Phase One demonstrated an increase in asthma prevalence in many low- and middle-income countries, while prevalence remained stable or decreased in many high-income countries (3,4). In North Macedonia, studies conducted among adolescents between 2002 and 2016 showed a divergent trend, with an increase in doctor-diagnosed asthma but a decrease in asthma-related symptoms, alongside persistent underdiagnosis (5).

The large differences in asthma prevalence and trends worldwide, as well as the rapid increase observed over recent decades, suggest that lifestyle and environmental factors play an important role. Genetic factors are unlikely to change substantially over such a short period of time. Studies examining environmental risk factors for asthma, including ISAAC and later research, have reported inconsistent findings, and the “Western lifestyle” has been suggested as one possible contributing factor. Differences in asthma diagnosis and treatment may also contribute to the observed variations (2,6–8).

Objective

The aim of this study was to assess the current prevalence of asthma and asthma-related symptoms among adolescents in Skopje and to examine changes between 2016 and 2026. We also compared these findings with the previously reported divergent pattern from 2002 to 2016 and examined changes in selected personal, family, behavioral, and environmental factors and their possible role in the observed trend.

Materials and Methods

The study was approved by the Ethics Committee for Human Research at the Faculty of Medicine in Skopje.

The 2026 survey was conducted in April and May and included 1,580 schoolchildren aged 6–15 from 16 randomly selected primary schools in Skopje. The inclusion criteria for the study were age and parental consent for participation. Children without parental consent or a completed questionnaire were, therefore, not included. Furthermore, children receiving corticosteroid or biological therapy for another disease, which could affect the interpretation of the results, were also excluded.

The present analysis was designed as a comparison of two repeated cross-sectional surveys among adolescents aged 12–15 years in Skopje. It included 690 participants from the 2016 survey and 323 from the 2026 survey, giving a total sample of 1,013 adolescents.

The same standardized questionnaire on respiratory health and asthma, developed at the University of Saskatchewan, Canada, was used in both surveys. (9,10) The questionnaire was completed as a written interview by the parent or guardian who was most familiar with the child's health, after providing informed consent. It included questions on respiratory symptoms, doctor-diagnosed asthma, use of

respiratory medication, and demographic, personal, family, perinatal, behavioral, and environmental factors.

To assess the changes in asthma prevalence, the 2026 findings were compared with corresponding data from the 2016 survey.

The analyzed outcomes included current asthma, ever doctor-diagnosed asthma, ever wheeze, wheeze in the past 12 months, wheeze causing sleep disturbance, wheeze limiting speech, exercise-induced wheeze, nocturnal dry cough, cough causing sleep disturbance in the absence of respiratory infections, and use of preventive anti-inflammatory therapy during the past 12 months.

Current asthma was defined as doctor-diagnosed asthma at any time in life combined with wheeze in the past 12 months and/or use of preventive anti-inflammatory therapy in the past 12 months.

The potential risk factors included paracetamol use, cat or dog domestic ownership, passive smoking at home, frequent truck traffic on the residential street, television viewing or video gaming for more than one hour per day, frequent fast-food consumption, household dampness, maternal and paternal asthma, and parental education.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 25.0 and JASP version 0.98.1.

For the calculation of the prevalence of asthma symptoms and doctor-diagnosed asthma, missing or other responses were included in the denominator. For the analysis of potential risk factors, only valid responses were included. (11)

Categorical variables were compared using Pearson's χ^2 test. Fisher's exact test was used when expected cell counts were small.

Associations between individual risk factors and asthma-related outcomes were first examined using binary logistic regression, with results presented as odds ratios (ORs) and 95% confidence intervals (CIs).

Multiple binary logistic regression was then used to assess the independent associations between the examined risk factors and asthma and asthma-related symptoms. Results are presented as adjusted odds ratios (aORs) with 95% CIs. The fully adjusted models included all examined risk factors simultaneously and were additionally adjusted for the survey year, age, and sex. The complete-case sample for these models included 787 participants.

Interaction analyses between the survey year and the selected risk factors (year $\times$ risk factor) were also performed to examine whether the strength of these associations differed between 2016 and 2026. Statistical significance was set at $p < 0.05$.

Results

The analysis included 1,013 adolescents aged 12–15 years: 690 from the 2016 survey and 323 from

the 2026 survey. The mean age was 12.94 ± 0.80 in 2016 and 12.80 ± 0.94 in 2026 ($p = 0.028$). Boys accounted for 50.1% of participants in 2016 and 49.2% in 2026 ($p = 0.802$).

Table 1 shows the prevalence of selected risk factors among adolescents in 2016 and 2026. In 2026, a cat or dog domestic ownership, frequent fast-food consumption, household dampness, parental history of asthma, and higher parental education were significantly more common. In contrast, spending more than one hour per day watching TV or playing video games was significantly less common. No statistically significant differences were found for paracetamol use, passive smoking at home, or frequent truck traffic on the residential street.

Table 1. Prevalence of selected risk factors among adolescents in 2016 and 2026

Factor	2016, n/N (%)	2026, n/N (%)	p
Paracetamol use in the past 12 months	479/670 (71.5%)	240/313 (76.7%)	0.088
Cat at home in the past 12 months	71/677 (10.5%)	92/268 (34.3%)	<0.001
Dog at home in the past 12 months	104/676 (15.4%)	111/282 (39.4%)	<0.001
Passive smoking at home in the past 12 months	221/688 (32.1%)	94/322 (29.2%)	0.349
Frequent truck traffic on the residential street on weekdays	254/686 (37.0%)	107/322 (33.2%)	0.241
TV/PC >1 hour/day	592/687 (86.2%)	170/323 (52.6%)	<0.001
Fast food >1 time/week in the past 12 months	311/678 (45.9%)	169/302 (56.0%)	0.004
Household dampness	63/680 (9.3%)	45/314 (14.3%)	0.017
Maternal asthma	12/657 (1.8%)	14/308 (4.5%)	0.015
Paternal asthma	7/656 (1.1%)	16/285 (5.6%)	<0.001
Higher maternal education	270/684 (39.5%)	274/320 (85.6%)	<0.001
Higher paternal education	346/682 (50.7%)	276/320 (86.2%)	<0.001

Percentages were calculated using valid responses for each risk factor. Unknown/invalid responses were excluded. p: Pearson's χ^2 test.

Table 2 shows the prevalence and ten-year trend of asthma and asthma-related symptoms in 2016 and 2026.

Table 2. Prevalence of asthma and asthma-related symptoms in 2016 and 2026

Outcome	2016 (N=690)	2026 (N=323)	p
Ever doctor-diagnosed asthma	19 (2.8%)	11 (3.4%)	0.568

Outcome	2016 (N=690)	2026 (N=323)	P
Current asthma	11 (1.6%)	8 (2.5%)	0.335
Ever wheeze	181 (26.2%)	84 (26.0%)	0.939
Wheeze in the past 12 months	38 (5.5%)	32 (9.9%)	0.010
Wheeze causing sleep disturbance	20 (2.9%)	35 (10.8%)	<0.001
Wheeze limiting speech	8 (1.2%)	13 (4.0%)	0.003
Exercise-induced wheeze	13 (1.9%)	20 (6.2%)	<0.001
Dry nocturnal cough in the absence of respiratory infection	66 (9.6%)	67 (20.7%)	<0.001
Dry nocturnal cough causing sleep disturbance, in the absence of respiratory infection	48 (7.0%)	51 (15.8%)	<0.001

p: Pearson's χ^2 test.

Doctor-diagnosed asthma and current asthma increased slightly, although the differences were not statistically significant. In contrast, current wheeze, exercise-induced wheeze, dry nocturnal cough, and all examined indicators of more severe current symptoms were significantly more common in 2026.

Tables 3 and 4 show the unadjusted and adjusted associations, respectively, between selected personal, family, environmental, and behavioral factors and the asthma-related symptoms whose prevalence changed significantly between 2016 and 2026.

Table 3. Unadjusted associations between selected risk factors and symptom outcomes — OR (95% CI)

Factor	Current wheeze	Sleep disturbance due to wheeze	Speech limitation due to wheeze	Exercise-induced wheeze	Dry nocturnal cough	Cough causing sleep disturbance
Paracetamol	2.27 (1.14–4.50)	2.14 (0.99–4.59)	2.11 (0.61–7.25)	0.98 (0.45–2.13)	1.14 (0.74–1.76)	1.10 (0.67–1.78)
Cat at home	2.06 (1.18–3.60)	2.73 (1.48–5.04)	2.45 (0.91–6.63)	2.26 (1.05–4.86)	1.31 (0.81–2.11)	1.28 (0.75–2.19)
Dog at home	0.97 (0.50–1.78)	1.34 (0.70–2.59)	2.24 (0.86–5.85)	1.05 (0.45–2.49)	1.45 (0.95–2.21)	1.29 (0.79–2.09)
Passive smoking at home	1.16 (0.70–1.94)	0.90 (0.50–1.64)	1.37 (0.56–3.33)	1.27 (0.62–2.62)	0.98 (0.66–1.46)	0.91 (0.57–1.43)
Frequent truck traffic	1.88 (1.15–3.10)	1.42 (0.82–2.45)	1.35 (0.56–3.24)	1.51 (0.75–3.04)	1.51 (1.05–2.19)	1.49 (0.98–2.27)

Factor	Current wheeze	Sleep disturbance due to wheeze	Speech limitation due to wheeze	Exercise-induced wheeze	Dry nocturnal cough	Cough causing sleep disturbance
TV/PC >1 hour/day	0.80 (0.47–1.40)	0.60 (0.34–1.06)	0.52 (0.21–1.27)	0.38 (0.19–0.76)	0.64 (0.43–0.95)	0.72 (0.46–1.14)
Fast food >1 time/week	1.44 (0.87–2.40)	1.33 (0.76–2.34)	1.04 (0.43–2.53)	2.03 (0.97–4.27)	1.87 (1.27–2.75)	1.54 (1.00–2.38)
Household dampness	5.06 (2.90–8.76)	3.42 (1.78–6.55)	3.66 (1.38–9.74)	2.29 (0.97–5.42)	1.82 (1.10–3.03)	1.88 (1.07–3.32)
Maternal asthma	4.17 (1.60–10.80)	2.37 (0.69–8.16)	1.84 (0.24–14.24)	4.24 (1.20–14.90)	2.07 (0.81–5.25)	3.01 (1.18–7.71)
Paternal asthma	1.34 (0.30–5.84)	0.82 (0.11–6.24)	2.15 (0.28–16.79)	3.03 (0.68–13.55)	1.96 (0.71–5.38)	2.12 (0.70–6.37)
Higher maternal education	1.29 (0.79–2.10)	2.14 (1.18–3.89)	2.15 (0.83–5.58)	2.72 (1.22–6.09)	1.26 (0.87–1.82)	1.31 (0.86–2.01)
Higher paternal education	1.66 (0.96–2.90)	2.43 (1.23–4.78)	2.32 (0.77–7.05)	1.51 (0.69–3.32)	1.40 (0.94–2.07)	1.41 (0.90–2.21)

OR = odds ratio; CI = confidence interval. Reference category: absence of exposure; for parental education, $\leq$ secondary education.

Table 4. Adjusted associations between selected risk factors and symptom outcomes — aOR (95% CI)

Factor	Current wheeze	Sleep disturbance due to wheeze	Speech limitation due to wheeze	Exercise-induced wheeze	Dry nocturnal cough	Cough causing sleep disturbance
Paracetamol	2.40 (1.07–5.37)	2.43 (0.89–6.67)	2.57 (0.50–12.38)	0.85 (0.33–2.21)	1.08 (0.64–1.84)	1.11 (0.60–2.02)
Cat at home	1.80 (0.84–3.84)	1.14 (0.40–3.21)	0.51 (0.08–3.23)	1.07 (0.30–3.75)	0.70 (0.34–1.42)	0.73 (0.30–1.64)
Dog at home	0.70 (0.32–1.54)	0.88 (0.32–2.38)	2.46 (0.61–9.85)	1.01 (0.32–3.24)	1.21 (0.68–2.18)	1.09 (0.55–2.20)

Factor	Current wheeze	Sleep disturbance due to wheeze	Speech limitation due to wheeze	Exercise-induced wheeze	Dry nocturnal cough	Cough causing sleep disturbance
Passive smoking at home	1.21 (0.63–2.32)	0.70 (0.29–1.67)	0.54 (0.13–2.21)	0.76 (0.27–2.12)	1.03 (0.61–1.71)	0.85 (0.47–1.50)
Frequent truck traffic	1.76 (0.95–3.24)	1.37 (0.63–3.00)	0.91 (0.26–3.13)	1.27 (0.50–3.24)	1.59 (0.99–2.55)	1.99 (1.16–3.40)
TV/PC >1 hour/day	0.44 (0.21–0.94)	0.62 (0.24–1.58)	0.40 (0.11–1.51)	0.23 (0.08–0.64)	0.83 (0.46–1.52)	0.81 (0.41–1.60)
Fast food >1 time/week	1.36 (0.74–2.49)	1.73 (0.81–3.71)	0.72 (0.22–2.39)	2.70 (1.04–7.01)	1.92 (1.20–3.10)	1.75 (1.02–2.90)
Household dampness	5.96 (3.01–11.80)	4.08 (1.72–9.64)	3.91 (1.05–14.50)	2.38 (0.75–7.62)	2.17 (1.18–3.99)	2.03 (1.02–4.00)
Maternal asthma	5.56 (1.76–17.50)	2.57 (0.63–10.50)	2.07 (0.20–18.82)	8.01 (1.86–34.50)	2.63 (0.93–7.43)	3.98 (1.40–11.50)
Paternal asthma	0.72 (0.12–4.50)	0.47 (0.05–4.44)	1.79 (0.20–19.57)	2.21 (0.39–12.50)	1.48 (0.43–5.10)	1.26 (0.31–5.10)
Higher maternal education	0.69 (0.32–1.48)	0.53 (0.20–1.41)	0.49 (0.11–2.31)	1.07 (0.31–3.72)	0.56 (0.30–1.02)	0.56 (0.28–1.10)
Higher paternal education	1.45 (0.69–3.07)	1.55 (0.60–4.02)	1.81 (0.42–7.88)	0.80 (0.24–2.64)	1.04 (0.59–1.83)	1.24 (0.65–2.40)

aOR = adjusted odds ratio; CI = confidence interval. All risk factors were entered simultaneously, and models were additionally adjusted for survey year, age, and sex (complete-case n=787). Reference category: absence of exposure; for parental education, $\leq$ secondary education.

After adjustment in the multiple logistic regression models, household dampness was consistently associated with several asthma-related symptoms, including current wheeze, sleep disturbance and speech limitation due to wheeze, dry nocturnal cough, and cough causing sleep disturbance.

Maternal asthma was statistically significantly associated with current wheeze, exercise-induced wheeze, and cough causing sleep disturbance. However, these estimates had wide confidence intervals and, therefore, limited precision.

Frequent fast-food consumption was associated with exercise-induced wheeze, dry night cough, and cough causing sleep disturbance. Frequent truck traffic, used as an indicator of outdoor air pollution,

was significantly associated with cough-causing sleep disturbance. Borderline, but not statistically significant, associations were observed for current wheeze ($p = 0.071$) and dry nocturnal cough ($p = 0.057$).

Paracetamol use remained independently associated with current wheeze after adjustment for the other examined factors. For TV/PC use >1 hour/day, aOR values below 1 were found for current wheeze and exercise-induced wheeze.

To examine whether the associations between the selected risk factors and current asthma-related symptoms differed by survey year, interaction terms between survey year and selected risk factors (year $\times$ risk factor) were tested. No statistically significant interactions were found between 2016 and 2026. The strongest borderline finding was observed for the interaction between household dampness and survey year for exercise-induced wheeze ($p = 0.086$), but this did not reach statistical significance.

Table 5. Selected interaction analyses: survey year $\times$ risk factor

Interaction term	Symptom	Interaction OR (95% CI)	p
Paracetamol $\times$ year	Wheeze in the past 12 months	0.60 (0.15–2.40)	0.473
Truck traffic $\times$ year	Wheeze in the past 12 months	0.76 (0.28–2.04)	0.579
Truck traffic $\times$ year	Dry nocturnal cough	0.74 (0.35–1.59)	0.444
Fast food $\times$ year	Dry nocturnal cough	0.83 (0.38–1.83)	0.644
Household dampness $\times$ year	Wheeze in the past 12 months	0.99 (0.32–3.00)	0.980
Household dampness $\times$ year	Exercise-induced wheeze	0.21 (0.04–1.25)	0.086

Interaction models were adjusted for age and sex. $p > 0.05$ indicates that there was no statistical evidence that the strength of the association differed between 2016 and 2026.

Table 6. Persistence of asthma-related symptoms according to preventive therapy use among adolescents aged 12–15 years

Symptom	2016 without therapy n=673	2016 with therapy n=17	p	2026 without therapy n=256	2026 with therapy n=25	p
Wheeze in the past 12 months	32 (4.8%)	6 (35.3%)	<0.001	17 (6.6%)	14 (56.0%)	<0.001
Wheeze causing sleep disturbance	18 (2.7%)	2 (11.8%)	0.084	24 (9.4%)	10 (40.0%)	<0.001
Wheeze limiting speech	7 (1.0%)	1 (5.9%)	0.182	9 (3.5%)	4 (16.0%)	0.020
Exercise-induced wheeze	11 (1.6%)	2 (11.8%)	0.038	13 (5.1%)	6 (24.0%)	0.003

Symptom	2016 without therapy n=673	2016 with therapy n=17	p	2026 without therapy n=256	2026 with therapy n=25	p
Dry nocturnal cough	59 (8.8%)	7 (41.2%)	<0.001	50 (19.5%)	12 (48.0%)	0.004
Cough causing sleep disturbance	40 (5.9%)	8 (47.1%)	<0.001	38 (14.8%)	12 (48.0%)	<0.001

p: Fisher's exact test. Percentages were calculated within preventive therapy groups. In 2026, 42 adolescents with unknown/invalid preventive therapy status were excluded only from this analysis.

In both 2016 and 2026, asthma-related symptoms were more common among adolescents receiving preventive anti-inflammatory therapy. In 2026, the differences were statistically significant for all six symptoms examined.

Discussion

This study provides an updated assessment of the current prevalence and ten-year trend of doctor-diagnosed asthma, asthma-related symptoms, and changes in the risk-factor profile among adolescents aged 12–15, living in Skopje. The prevalence of doctor-diagnosed asthma remained low compared with the reported prevalence of childhood asthma in Europe of around 9% (12). Over the ten-year period, doctor-diagnosed asthma increased, although the difference was not statistically significant. At the same time, several current and clinically relevant asthma-related symptoms increased significantly. Underdiagnosis also remained an important problem, together with an unsatisfactory response to preventive anti-inflammatory therapy. In addition, changes in exposure to several environmental and lifestyle factors were observed during the ten-year period.

These findings are particularly important when compared with previous studies among adolescents in Skopje. Alas, repeated cross-sectional surveys conducted in 2002, 2006, and 2016 showed a divergent trend as follows: doctor-diagnosed asthma increased, whereas several asthma-related symptoms decreased (5). The current findings suggest that this pattern did not continue during the past decade. Instead, several asthma-related symptoms increased together with the increase in doctor-diagnosed asthma.

Our findings are consistent with results from four repeated surveys conducted among children in Poland between 1993 and 2014, where both asthma symptoms and diagnosed asthma increased, suggesting a real increase in asthma occurrence (13). A similar increase in current asthma attacks and diagnosed asthma was reported in the general population in Italy over a 25-year period (14).

However, trends have not been the same in all countries. Studies in Denmark showed stabilization of wheeze and asthma prevalence over a nine-year period, (15) while no further increase was observed among preschool children in Bavaria over eight years (16). In the Netherlands, a large study of children aged 5–18 years found a decrease in the incidence of diagnosed asthma after 2008 (17). In England, the prevalence of current doctor-diagnosed asthma decreased among children and adults younger than 45, while the use of preventive anti-inflammatory therapy and treatment of asthma exacerbations increased (18).

The ISAAC study also showed different trends across countries over 5–10 years periods. Asthma prevalence generally increased in many low- and middle-income countries, while it tended to stabilize or decrease in many high-income countries (3,4).

The parallel increase in asthma symptoms and their severity, together with the increase in doctor-diagnosed and current asthma, suggests a real increase in asthma among young adolescents in Skopje during the past ten years. At the same time, the much higher prevalence of asthma-related symptoms during the past 12 months compared with the prevalence of diagnosed and current asthma suggests that asthma remains underdiagnosed.

In the corresponding 2016 study among children aged 5–15 living in Skopje, only 14.9% of children with wheeze during the past 12 months had been diagnosed with asthma, although 73.6% of these children were receiving treatment for breathing problems. This pattern was similar to findings from Ukraine and Belarus, while the situation was considerably better in Canada and Poland (9). These findings suggest that, in addition to asthma being underdiagnosed, the diagnosis itself may sometimes be avoided by physicians and parents. Some children may instead be diagnosed with recurrent obstructive bronchitis and treated with preventive therapy.

In both 2016 and 2026, asthma-related symptoms were more common among adolescents receiving preventive anti-inflammatory therapy. In 2026, the differences were statistically significant for all six symptoms examined. This should not be interpreted as evidence that preventive therapy is ineffective. A likely explanation is confounding by indication: adolescents with more severe or persistent symptoms are more likely to be prescribed preventive treatment. Other possible explanations include lower-than-required doses, irregular or insufficiently long treatment, or incorrect inhaler technique.

In the multivariable analysis, household dampness was one of the factors most consistently associated with asthma-related symptoms. After adjustment for other potential risk factors, it remained associated with current wheeze, more severe wheeze causing sleep disturbance, wheeze limiting speech, dry nocturnal cough, and cough causing sleep disturbance. However, because of the cross-sectional design, these findings show associations and do not establish causality.

Frequent truck traffic on the residential street, used as an indicator of outdoor air pollution, was associated only with current severe cough causing sleep disturbance. This is similar to a previous finding from Skopje, where truck traffic was also identified as a risk factor for current wheeze (19). Traffic-related air pollution has also been identified as a risk factor for asthma internationally (12).

Frequent fast-food consumption was positively associated with exercise-induced wheeze, dry nocturnal cough, and cough causing sleep disturbance during the past 12 months, in line with findings from ISAAC and other studies (12,20). Paracetamol use was positively associated with current wheeze. Similar associations between paracetamol use and asthma symptoms have been reported in previous local and international studies (21–23).

When we examined whether the associations between the risk factors and current asthma symptoms varied by survey year, there was no statistical evidence that the strength of these associations between 2016 and 2026. Diagnosis and treatment practices in our setting may, therefore, be among the factors contributing to the observed asthma trend.

An important strength of this study is the repeated cross-sectional design in the same geographical area and age group, using the same standardized questionnaire. The main limitations are the use of questionnaire-based data, the possibility of response bias, and the inability to establish causal relationships because of the cross-sectional design. In addition, detailed information on adherence to preventive therapy, inhaler technique, treatment dose, and duration was not available.

Conclusion

Among young adolescents in Skopje, asthma showed an increasing trend over the last ten years, accompanied by a significant increase in several asthma-related symptoms. Asthma remains underdiagnosed, and the findings also indicate problems with adequate preventive treatment.

These results highlight the need for better education of healthcare professionals to improve the recognition, diagnosis, and treatment of asthma. Education of patients and parents is also important, particularly regarding the regular and correct use of prescribed preventive therapy.

Declarations

Ethics approval and consent to participate: The study was approved by the Ethics Committee of the Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, on 14 February 2026.

Informed consent: Written informed consent was obtained from the parents or legal guardians of all children who took part in the study. Participation was voluntary, and all collected data were kept confidential.

Conflict of interest: The authors declare no conflict of interest.

Funding: This research received no external funding.

Availability of data and materials: The data used in this study are available from the corresponding author upon reasonable request.

Authors contributions: All authors read and approved the final manuscript.

Artificial Intelligence (AI) statement: No AI tools were used in the preparation of this manuscript.

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ASSESSMENT OF RIGHT VENTRICULAR HEART FUNCTION IN POLYTRAUMATIZED PATIENTS WITH PULMONARY CONTUSIONS WITH AND WITHOUT NEED FOR MECHANICAL VENTILATION: A MULTICENTER STUDY PROTOCOL

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Abstract

Introduction: Pulmonary contusions are the most common form of chest trauma (25-80%) with a mortality rate of 10-20% in severely injured patients, while ARDS has been observed in 78% of polytraumatized patients with pulmonary contusions. Right ventricular function has already been evaluated in patients with acute respiratory failure and ARDS, with studies demonstrating a clear association between lung injury and the development of right heart dysfunction.

Study Objective: The aim of this study is to examine the relationship of right ventricular dysfunction and the usage of mechanical ventilation in patients with pulmonary contusions.

Material and Methods: In this prospective cohort study, right ventricular function will be evaluated by echocardiography at 4 examination points. Measurements will include RV diameters, tricuspid regurgitation velocity, TAPSE, RV Fractional Area Change, RV diastolic function and Inferior Vena Cava collapsibility or distensibility. Pulmonary circulation pressures will be calculated in both groups using established equations based on echocardiography-derived measurements. All patients included in the study must be polytraumatized with radiologically confirmed existence of pulmonary contusions and will be divided into two groups depending on the need for mechanical ventilation.

Rationale: Beyond the primary objective of the study, this detailed explanation of the protocol, originally developed as part of a completed and defended PhD thesis, is intended facilitate multicenter collaboration and further research into the effects of mechanical ventilation on right ventricular function.

Keywords: Echocardiography; Lung ultrasound; Mechanical ventilation; Pulmonary contusions; POCUS; Right ventricular dysfunction.

Introduction

Pulmonary contusions are defined as destruction of the lung parenchyma with the occurrence of alveolar hemorrhage as a result of blunt thoracic trauma without pleural laceration and are present in 17-75% of blunt thoracic trauma (1). The presence of pulmonary contusion in polytraumatized patients is a serious predictor of mortality in up to 10-25% (1). According to Hosseini M. and colleagues, lung contusions are the most common form of chest trauma (25-80%) with a high mortality rate of 10-20% in severely injured patients (2). Following trauma involving the transfer of kinetic energy on the lung, the secondary lung injury occurs, which is considered to be immunologically mediated due to activation of defensive immune mechanisms. The systemic inflammatory response is marked by the secretion of IL-6, which is a mediator of lung injury after the occurrence of trauma. Kurt A. et al. found that IL-6 levels are significantly higher in patients with lung contusions compared to the control group (3). The occurrence of lung contusions disrupts gas exchange at the level of the alveolo-capillary membrane, an increase in pulmonary vascular resistance, and a decrease in lung compliance in the first 24 hours after injury (4). Lung contusions are considered as an independent risk factor for the occurrence of Acute Lung Injury - ALI and Acute Respiratory Distress Syndrome – ARDS. ARDS has been observed in 17% of patients with an isolated lung contusion and in 78% of patients with lung contusion accompanied by polytrauma. (5). Impaired gas exchange resulting from lung injury leads to hypoxemia, which triggers defense mechanisms such as hypoxic pulmonary vasoconstriction, thereby increasing pulmonary circulation resistance. In addition, an immunologically mediated increase in vascular permeability promote transmigration of fluid and leukocytes into the interstitium, and subsequently into the alveoli, contributing to an increase in right ventricular afterload. In an experimental animal study, where oxygen delivery was reduced with a fall in FiO_2 from 0.3 to 0.15, a 100% increase in mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR), confirmed that hypoxemia can lead to an increase in right ventricular (RV) afterload (6). Hypoxic vasoconstriction and the need for mechanical ventilation with high PEEP can compromise RV function in individuals with acute respiratory failure, where excessive alveolar distension can occur due to the application of high tidal volumes, which can lead to an increase in RV afterload (7). An increase in RV afterload due to an increase in pulmonary vascular resistance (PVR) as a form of right ventricular pressure load leads to a series of adaptive or maladaptive structural and functional changes in the right ventricle, which is why mechanical ventilation and lung injury are thought to play an important role in the development of right ventricular dysfunction (RVD) (8).

Right Ventricular Dysfunction: Definition and Clinical Significance in Critically Ill Patients

Right ventricular dysfunction refers to impaired RV systolic and/or diastolic performance resulting from the inability of the right ventricle to adequately adapt to changes in preload, afterload, or myocardial contractility. Progression to right ventricular failure occurs when the RV is unable to maintain sufficient pulmonary blood flow and adequate left ventricular filling (11). A high mortality rate of 32-61% was found in patients diagnosed with right ventricular failure. An acute increase in RV afterload is considered the most frequently recorded reason for RVD development, and the transition from RVD to RV failure depends on the RV ability to adapt to the increased RV afterload (11). RVD is the result of disturbed RV mechanics that cannot deliver blood in the pulmonary circulation against the increased RV afterload (12). When, for any reason, there is an increase in pressure in the pulmonary circulation, a pressure load occurs on the right ventricle, which activates the adaptive mechanisms that aim to ensure an adequate stroke volume. However, when the pressure load exceeds the adaptive

capacities of the right ventricle, right heart dysfunction occurs. When the pressures in the pulmonary circulation are elevated, myocardial cell growth is activated in RV, initiating the process of hypertrophy of the free wall of the right ventricle, which, according to Laplace's law, should resist the right ventricular afterload and provide an adequate stroke volume (12). When this compensatory mechanism is worn out and the right ventricle is not able to achieve an adequate stroke volume against the pressure in the pulmonary circulation, the next adaptive mechanism occurs, i.e., the right ventricular dilatation and thinning of the septal wall, leading to echocardiographic signs of right heart dysfunction with elevated dimensions. Because of its design and function to generate stroke volume against a pulmonary circulation with low pressures and high compliance, the right ventricle tolerates volume than pressure load more easily. If right ventricular afterload increases gradually over an extensive period, the ventricle can hypertrophy, remodel and adapt to the increased pressure load, and it will successfully tolerate higher values of sPAP (systolic pulmonary artery pressure). However, an acute increase in the right ventricular afterload without previous right ventricular hypertrophy will prevent the right ventricle from generating sPAP higher than 50-60mmHg, leading to the development of signs of RVD (13,14). According to Chen et al., as many as 43% of examined 1879 critically ill patients had RV dysfunction (15); while Grignola JC and Domingo E consider that RVD occurs in as many as 30-56% of patients with ARDS even when protective modes of mechanical ventilation are used, and the occurrence of RVD is directly influenced by the severity of lung injury and the ventilatory strategy (16). The $\text{PaO}_2/\text{FiO}_2$ ratio below 150, $\text{PaCO}_2 > 48\text{mmHg}$ (6.4 kPa), and driving pressure greater than 18 in critically ill patients, are identified as risk factors for the occurrence of RVD (16). Lanspa et al., reported that the development of RVD is an indicator of the severity of lung disease and is associated with increased 28-day mortality and lower values for the $\text{PaO}_2/\text{FiO}_2$ ratio in critically ill patients, but not with the need for mechanical ventilation (17). RVD in this research will be defined as the existence of abnormal values for at least one of the following markers for the assessment of right ventricular function: for TAPSE values less than 17mm, RV FAC < 35% and/or RV/LV ratio > 1.

Rationale for the Use of Ultrasonography in the Diagnosis and Monitoring of Pulmonary Contusions

Given the fact that chest x-ray can underestimate the severity of blunt thoracic trauma and the presence of pulmonary contusions, computed tomography is considered the gold diagnostic standard. Computed tomography, in addition to exposure to high doses of X-rays, carries the risk of complications that may occur during the transport of critically ill patients, especially those needing mechanical ventilation. Therefore, ultrasonography can be an adequate alternative for diagnosing lung contusions and detecting their extent (18). In their study, Mohamed SS. et al. examined the accuracy of ultrasound in detecting lung contusions and assessing their extent compared to CT, as well as the predictive power of the ultrasonographic findings for the development of ARDS. LUS study, performed within 72 hours from injury can accurately indicate a high risk for the development of ARDS in patients with lung contusions. Also, the LUS findings on the extent of pulmonary contusions correlated with the findings of the performed CT examinations (18), which points to the fact that LUS can be used for the diagnosis and monitoring of the evolution of pulmonary contusions as well as the assessment of their extent. In a study, Jahanshir A. and colleagues examined the LUS accuracy, and found that lung contusions can be diagnosed with PoCUS with a sensitivity of 58, 1% and a specificity of 100% with a positive predictive value of 100% and a negative predictive value of 86.3% (19). According to Zhao Z. et al., LUS performed early in the course of hospitalization, after the first 24 hours, is a more reliable diagnostic indicator of ALI than subsequent follow-up examinations (20). LUS not only has

a positive correlation with the level of EVLW and $\text{PaO}_2/\text{FiO}_2$, but it is also considered a diagnostic marker and predictor of mortality in patients with ARDS (20). Another study by D. Huang et al., which included 55 patients treated in ICU with suspected ARDS, showed that LUS findings on the first, second and third days of hospitalization correlated with CT findings in patients with ARDS, but also in patients where ARDS was not present (21). The study by Lei Li et al. found that LUS findings on the first day positively correlate with the height of SOFA Score and APACHE II, while there is a negative correlation with $\text{PaO}_2/\text{FiO}_2$ (22). Therefore, as the lung injury progresses over the following days, the LUS score increase while the $\text{PaO}_2/\text{FiO}_2$ ratio decreases. This suggests that LUS with a 12-field view and a 0-36-point score represents a semiquantitative tool in lung injury monitoring. Baseline LUS Score is an independent risk factor for 28-day mortality in patients with ALI, as well as SOFA score, APACHE II score, and $\text{PaO}_2/\text{FiO}_2$ (22). LUS Score, APACHE II, SOFA, and $\text{PaO}_2/\text{FiO}_2$ combined together can predict the prognosis of patients with ALI with 88.9% sensitivity and 95.5% specificity (22). LUS as a diagnostic method for the etiology of respiratory failure is superior to radiography and clinical examination (23-25). Findings obtained from LUS can be compared with those obtained from computed tomography (26, 27). Costamagna Andrea et al compared CT and LUS results at admissions and one week later to determine whether LUS can adequately monitor the developmental dynamics of lung changes. They concluded that LUS results correlate with CT results at admission, and one week later, suggesting that LUS can be used to monitor the evolution of lung changes in patients with ARDS (28). Stengel D. et al performed a meta-analysis that included a total of 34 studies with 8635 subjects on the use of POCUS in the diagnosis of blunt thoracoabdominal trauma and found that this method can diagnose chest injuries with a sensitivity and specificity of 96%. and 99% respectively (29). The European Society of Intensive Care Medicine (ESICM) issued a strong recommendation regarding the use of ultrasound in ICU, identifying the detection of B-lines as indicators of interstitial syndrome. Therefore, consolidation as a form of lung aeration disorders should be considered as a basic competency for every intensivist (30), justifying the use of LUS in this study.

Rationale for the Use of Echocardiography in Assessing Right Ventricular Function in Critically Ill Patients with Lung Injury

The ESICM strongly recommends the use of echocardiography as a method for evaluating right ventricular function and diagnosing right ventricular failure, by measuring right ventricular diameter, RV/LV ratio, right ventricular free wall thickness, and right ventricular chamber end-diastolic diameter. These should be basic competencies of the intensivist, necessary for the diagnosis of right heart failure in critically ill patients (30). According to Riishede M, POCUS leads to rapid rejection of presumptive diagnoses in the first 4 hours of hospitalization, and increases the chances of receiving adequate treatment in the first 4 hours by 13.5% (31). C. Lazzeri and colleagues also favor the use of combined ultrasound of the heart and lungs. This conclusions corresponds with the findings of their study in which 47 patients with ARDS due to COVID-19 were examined, where in addition to LUS, the patients were examined echocardiographically with special reference to the right ventricular function with increased right ventricular afterload. RV/LV ratio, right ventricular end-diastolic diameters, right ventricular free wall thickness, tricuspid annular systolic excursion (TAPSE), and systolic pulmonary arterial pressure (sPAP) were monitored. It was determined that non-survivors had higher LUS values at admission, increased RV/LV ratio, and higher sPAP values compared to survivors. In addition, this study demonstrated a correlation between the value of LUS score and the measured sPAP, supporting the routine combined assessment of cardiac and pulmonary function in critically

ill patients. The development of ARDS and pulmonary deaeration increase the pulmonary vascular resistance, which, together with the mechanical ventilation, increases RV afterload and precipitates RVD (32). Vignon P et al. also recommend the combined use of lung ultrasound and echocardiography in critically ill patients with ARDS, as increased pulmonary arterial pressure from lung injury and the need for mechanical ventilation can compromise RV function (33). The risk of developing acute right heart failure in patients with ARDS is highest in the first three days after being placed on mechanical ventilation (34). The first echocardiographic examination in patients with ARDS on mechanical ventilation should be performed within the first 24 hours after admission (33). The rationale behind the use of echocardiography as a method in this study and in daily clinical practice is confirmed by the results of a study performed on 700 patients with ARDS, who were divided into two groups: patients who had no signs of right heart disease and were hemodynamically stable; and hemodynamically unstable patients who did not necessarily have echocardiographic signs of right heart disease. Echocardiography was repeated at least once a day in the second group of patients, but also in patients who will developed hemodynamic instability and/or hypoxia de novo (35).

Study Objective

According to C. Chen et al., up to 43% of the 1879 examined critically ill patients had ventricular dysfunction (36). So far, right ventricular function has been evaluated in patients with acute respiratory failure and ARDS, and a clear relationship between lung injury or ARDS and the development of right heart dysfunction has been established (7,37,38,39). RVD has also been detected in patients with sepsis (8,40,41). The literature has analyzed the association between right heart failure and acute respiratory failure in general, without considering blunt traumatic lung injury as a separate entity. Traumatic chest injury occurs in almost 60% of all polytrauma patients and has a high mortality rate of 20-25% (42). Lung contusions occur in 17-75% of blunt chest injury cases followed by rib fracture (43). The rationale for evaluating right ventricular function in polytraumatized patients with pulmonary contusions arises from the fact that lung injury and hypoxemia lead to pulmonary hypoxic vasoconstriction, which, together with the use of mechanical ventilation, can have deleterious effects on the RV. The association between the occurrence of right ventricular dysfunction in polytraumatized patients with pulmonary contusions and the need for mechanical ventilation could influence the therapeutic approach and the course of treatment in regards to timely diagnosis and treatment of RVD by applying protective modes of ventilation. Therefore, it is crucial to evaluate the right ventricular function in patients with pulmonary contusions because the lung injury by itself, and often the therapeutic strategies involving mechanical ventilation, can generate greater afterload due to the increase in pulmonary circulation pressures. Pressure overload caused by the above-mentioned causes can lead to right ventricular adaptation or maladaptation resulting in altered right ventricular function. Due to its structural characteristics, the right ventricle cannot maintain optimal function when faced with increased afterload, which in 48 hours will change the structural and functional echocardiographic parameters (44), justifying the evaluation of right ventricular function in patients with a traumatic model of lung injury. Hence, we hypothesize that the use of mechanical ventilation in polytraumatized patients with pulmonary contusions is associated with the development of right ventricular dysfunction. In addition to the primary hypothesis, this study has several other objectives, which are discussed below:

- To determine the association between the usage of mechanical ventilation and the development of right ventricular dysfunction

- To determine the overall prevalence of RVD in polytraumatized patients with pulmonary contusions, and the prevalence of RVD in patients who are treated with mechanical ventilation versus those who are not treated with mechanical ventilation
- To determine the time frame of myocardial vulnerability when the risk of developing RVD is the highest in both groups.
- To determine the length of hospital stay (Length of stay-LOS), the length of stay in the intensive care unit (ICU Length of stay - ICU LOS) in both studied groups
- To determine the number of days spent without the need for mechanical ventilation (VFD– Ventilator free days) in the group of patients treated with mechanical ventilation who will develop RVD, compared to those who will not develop RVD
- To determine mortality in both study groups as well as in patients who will develop RVD versus those who will not develop RVD
- To analyze the parameters of mechanical ventilation in patients who will develop RVD versus those who will not develop RVD and thereby reveal the existence of a possible association between the development of RVD and any of the analyzed parameters
- To evaluate the correlation of measured LUS and the sPAP levels
- To evaluate echocardiographically estimated pulmonary arterial pressures in both groups and compare them between patients who develop RVD and those who do not
- To evaluate the association of LUS, TAPSE, pulmonary pressures with development of RVD, mortality and LOS
- To evaluate the utility of combined bedside lung and cardiac ultrasonography (POCUS) and its potential integration into routine clinical practice

As this protocol was originally developed as part of a completed PhD thesis, its publication is intended to encourage further multicenter research involving institutions across the country and the wider region. The study has already been conducted using this protocol, with 81 patients enrolled over a two-year period. Since the study's specific inclusion and exclusion criteria limit the number of eligible patients, we believe that involving other research centers may significantly contribute in recruiting another 100 patients in a timeframe of another 2 years. Multicentric involvement is expected to include a significant number of patients so that its statistical significance may increase. Apart from the call for multicentric involvement in this study, researchers are encouraged to use this protocol when evaluating the effect of mechanical ventilation over the right ventricle in critically ill patients, even if they experience different kind of underlying condition demanding mechanical ventilation, other than pulmonary contusions.

Materials and Methods

Study Design

This study is prospective, cohort, and observational in design. Written informed consent for participation in the original single-center study was obtained from the patients or their legally authorized representatives, as applicable. The study was approved by the Ethics Committee of the Faculty of Medicine in Skopje and the Ethics Commission at the Department of Anesthesiology, Reanimation and Intensive Care, as relevant institutional Ethics Committees. Any future multicenter implementation of this protocol should be conducted following approval by the respective local Ethics Committees and according to applicable requirements for informed consent at each participating center.

Sample

The original study was already conducted at the University Clinic for Traumatology, Orthopedics, Anesthesiology, Reanimation, Intensive Care, and Emergency Department and included 81 patients who met the predefined inclusion criteria. For future multicenter application of this protocol, eligible patients will be allocated to the MV and non-MV groups, based on the need for mechanical ventilation. Patients initially enrolled in the non-MV group who subsequently require mechanical ventilation for any reason during hospitalization are excluded from the study.

Inclusion Criteria:

- patients must be older than 18 years
- patients where the existence of pulmonary contusions is determined by a radiologist using a CT scan before admission in the ICU
- patients for whom signed informed consent is provided by a family member

Exclusion Criteria:

- patients with pneumothorax due to the inadequacy of examining the lung with ultrasound.
- patients with a history of stent placement or CABG
- patients with previously echocardiographically proven pulmonary arterial hypertension and/or reduced left ventricular systolic function, i.e. previously diagnosed right heart disease
- patients with a history of COPD or idiopathic pulmonary fibrosis
- patients who were resuscitated prior to admission in the ICU
- patients with elevated levels of Troponin suggesting cardiac contusion
- pregnant women.

Methods

All patients included in the study will be examined in four unified time points, the first examination will be performed within 24 hours after the patient's admission, the second on the 4th day of hospitalization, the third examination will be done on the 7th day from the hospitalization, and the fourth examination will be performed on the 14th day of the patient's admission. In all patients, an ultrasonographic examination of the lungs, echocardiography, standard laboratory analyses, acid-base status will be performed, and vital parameters and mechanical ventilation parameters will be noted identically as it was done in the first cohort of 81 patients. Placing patients on mechanical ventilation will be performed based on the generally accepted criteria for intubation and mechanical ventilation such as: presence of hypoxia with SpO_2 below 90%, i.e. $\text{PaO}_2 < 60 \text{ mmHg}$, presence of hypercapnea with $\text{PaCO}_2 > 55 \text{ mmHg}$, respiratory rate > 35 per minute, hemodynamic instability with systolic pressure lower than 90 mmHg accompanied by signs of shock, as well as the presence of impaired consciousness with $\text{GCS} \leq 8$. To avoid bias, the author of this research will not participate in setting the indication for starting mechanical ventilation nor will he participate in ordination of the parameters of mechanical ventilation. All patients with elevated levels of troponins measured 4 hours after ICU admission will not be included in the study because of possible cardiac contusion.

Ultrasonographic Examination of the Lungs

All patients that will be recruited in this study after the first 24 hours of patient admission, on days 4, 7, and 14, will undergo ultrasonographic examination of the lungs. Lung ultrasound examination will include standardized assessment of pulmonary aeration using a 12-region Lung Ultrasound Score (LUS), with each region scored from 0 to 3 in line with the degree of aeration loss. Where clinically appropriate, elements of the BLUE protocol may additionally be used for bedside assessment of acute respiratory abnormalities (45). Lung injury will be stratified according to the Lung Ultrasound Score (LUS). Both of the patients' lungs will be evaluated, by dividing them into 12 segments: anterior-upper, anterior lower segment left and right, lateral upper, lateral lower segment left and right, and posterior upper and posterior lower segment left and right. The ultrasound finding of the lung parenchyma will be interpreted and classified as follows: the presence of A-lines indicating a normally aerated lung will be scored 0 points, the presence of 3-5 B-lines described as laser light or sunlight that extend from the surface to the bottom of the screen and are clearly defined by the surrounding parenchyma will be scored with 1 point, the presence of multiple B-lines or their confluence will be scored with 2 points, the existence of clearly circumscribed pulmonary consolidations where lung parenchyma resembling a liver will be scored with 3 points (46). Examination of the lung will be made with positioning of the probe perpendicularly to the ribs where the lung parenchyma in between two ribs will be visualized and examined. All previously mentioned regions will be scored as it was already explained and each of their points will provide the total number of the LUS Score. The minimum number of the total LUS Score will be 0 points, indicating a completely preserved lung aeration and structure, while the maximum number of points for the LUS Score can reach 36 points, indicating a serious lung injury leading to its deaeration. For scanning of the lungs, a convex probe with a frequency of 2.5-7.5MHz will be used.

Echocardiographic Examination

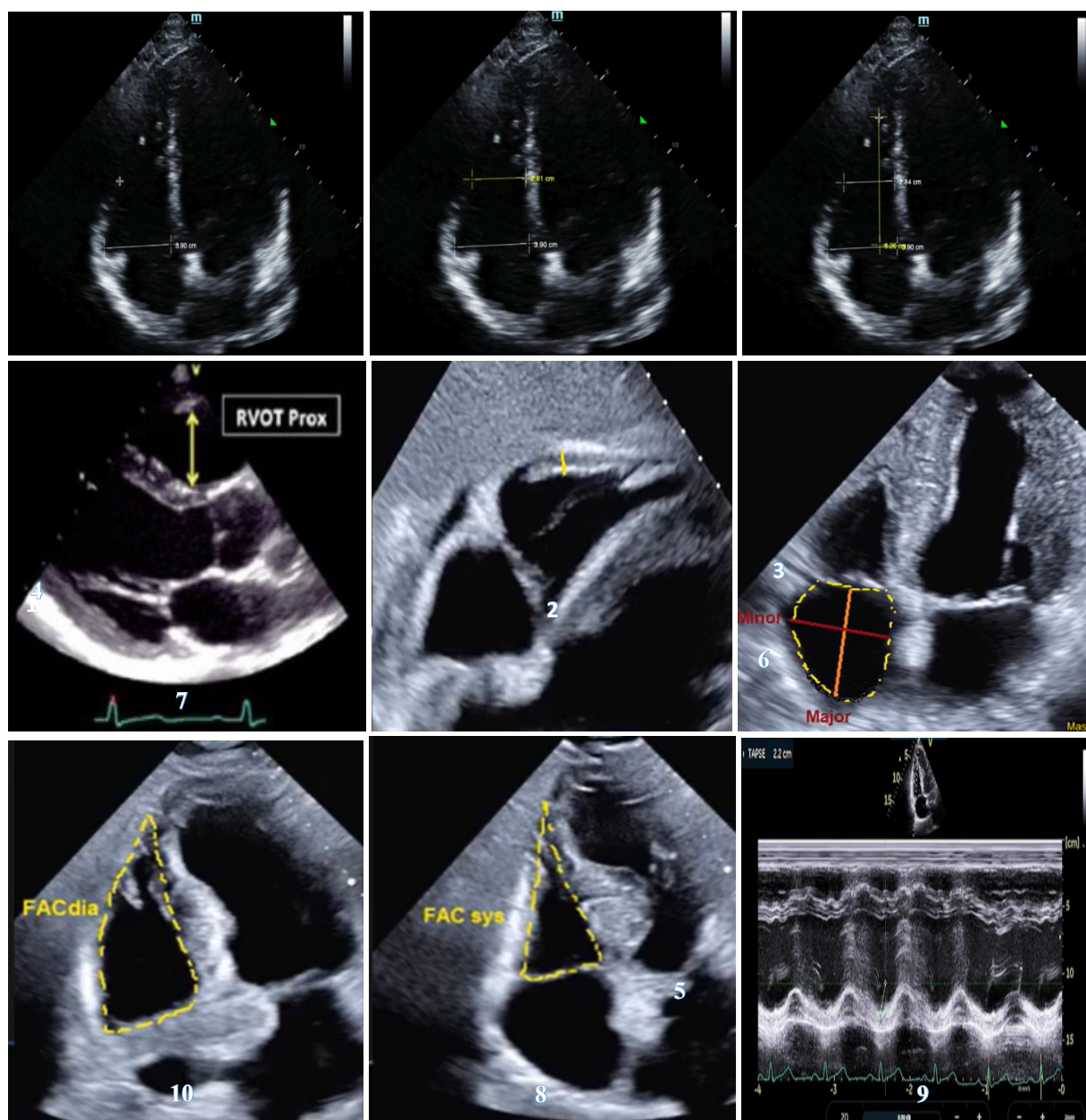
All patients that will be recruited in the future will have an echocardiographic examination focusing

on right heart function after the first 24 hours of admission, on the 4th day of admission, on the 7th day of admission, and on the 14th day of admission. The evaluation of right ventricular dimensions, systolic and diastolic function will be performed following the recommendations for echocardiographic evaluation of cardiac cavities issued in 2015 by the American Society of Echocardiography and the European Association of Cardiovascular Imaging (47). In order to rule out pre-existing left ventricular dysfunction before inclusion in the study, the left ventricular surface in end diastole and end systole (LVEDA and LVESA) will be measured and the area of fractional change of the left ventricle (LV FAC) will be calculated according to formula $LVEDA-LVESA/LVEDA \times 100$, whereby patients with LV FAC less than 35% will be excluded from the study. During each echocardiographic examination, the dimensions of the right ventricle in end diastole will be measured as: basal RVD (diameter of the RV at the base of the heart), midRVD (dimension of the RV at the middle segment), longRVD (longitudinal diameter of the RV) measured in an apical 4 chamber view of the heart where values for bRVD > 41mm, values for midRVD > 35mm and lRVD > 83mm suggest right ventricular dilatation (47,48). The diameter of the RV outflow tract (RVOT) in end diastole, as well as the free wall thickness of the right ventricle will be measured in the long parasternal axis, and measured values for RVOT > 35mm will suggest dilatation, while values for the free wall greater than 5mm will be considered as hypertrophic (47,48). Furthermore, using the apical 4-chamber view of the heart, the area of RV in end diastole (RVEDA) and in end systole (RVESA) will be measured, whereas the value for the fractional change of RV surface (RV FAC) will be calculated according to the following formula: $RVEDA-RVESA/RVEDA \times 100$ as an indicator of the radial function of the RV and it will be expressed in percent; while values for RV FAC < 35% will define the existence of RVD (47,48). Evaluation of the longitudinal systolic function of the RV will be performed using the apical four-chamber window in which the tricuspid transannular excursion in systole (TAPSE) will be evaluated in M-mode with the cursor positioned in the direction of the tricuspid lateral annulus with values for TAPSE less than 17 mm suggesting the existence of RV systolic dysfunction (47,48). During the echocardiographic examination, the presence of tricuspid regurgitation will be detected with color Doppler, and its quantification of peak tricuspid regurgitant velocity will be done with CW Doppler. The systolic pulmonary pressure will be calculated according to the modified Bernoulli equation where sPAP is equal to $\text{peak tricuspid regurgitant velocity}^2 \times 4 + \text{right atrial pressure (RAP)}$ (48,49). Using CW Doppler Pulmonary artery regurgitant flow, the velocity will be measured. Its maximal value will be used for dPAP calculation according to this equation: $\text{peak pulmonary valve regurgitant velocity}^2 \times 4 + \text{right atrial pressure (RAP)}$. Mean PAP (mPAP) should be calculated by using the following equation: $\text{sPAP} \times 0.61 + 2$. RAP should be measured by standard central venous line or it may be calculated when measuring the maximal and minimal values of the Inferior Vena Cava used for calculating the IVC collapsibility or distensibility depending of the need of mechanical ventilation. At each examination, the diastolic function of both ventricles will be evaluated using PW Doppler and the result will be recorded as the E/A ratio. The E' wave will be monitored with tissue Doppler. The obtained values for the left ventricular E wave and the E' wave will provide their ratio, which will be calculated according to the following formula E/E' . The result will be considered as the left preload pressure (LAP) whose value corresponds to the pulmonary capillary wedge pressure (PCWP), which can be corrected according to Nagueh's formula where $\text{PCWP} = 1.9 + 1.24(E/E')$ (50). The regurgitant jet from the pulmonary artery (PR Vmax) PA regurgitant peak velocity with CW Doppler will also be evaluated and from the obtained values the diastolic pressure in the pulmonary circulation (dPAP) will be calculated according to the following formula: $\text{PRVmax}^2 \times 4 + \text{RAP}$. The mean pressure in the pulmonary circulation will be calculated according to the following formula $\text{sPAP} \times 0.61 + 2$ (48,49). Dimensions, collapsibility or distensibility of the inferior vena cava, and the

dimensions of the right atrium will also be measured (47,48).

Remaining Investigations

In addition to the ultrasonographic parameters of the patients included in the study, the following will also be monitored: mortality, length of hospital stay (LOS - length of stay), length of ICU stay (ICU LOS) and number of days without mechanical ventilation (ventilator free days). Basic vital parameters such as systolic and diastolic arterial pressure, mean arterial pressure (MAP), heart rate and blood oxygen saturation (SpO_2) will be monitored in all patients. Central venous pressure (CVP) will be measured in each patient, and if direct measurement is not possible, it will be indirectly calculated by the values of the dimensions of the inferior vena cava and its collapsibility (47,48). Acute Physiology and Chronic Health Evaluation II (APACHE II) Score, Sequential Organ Failure will be evaluated in each patient enrolled in the study.



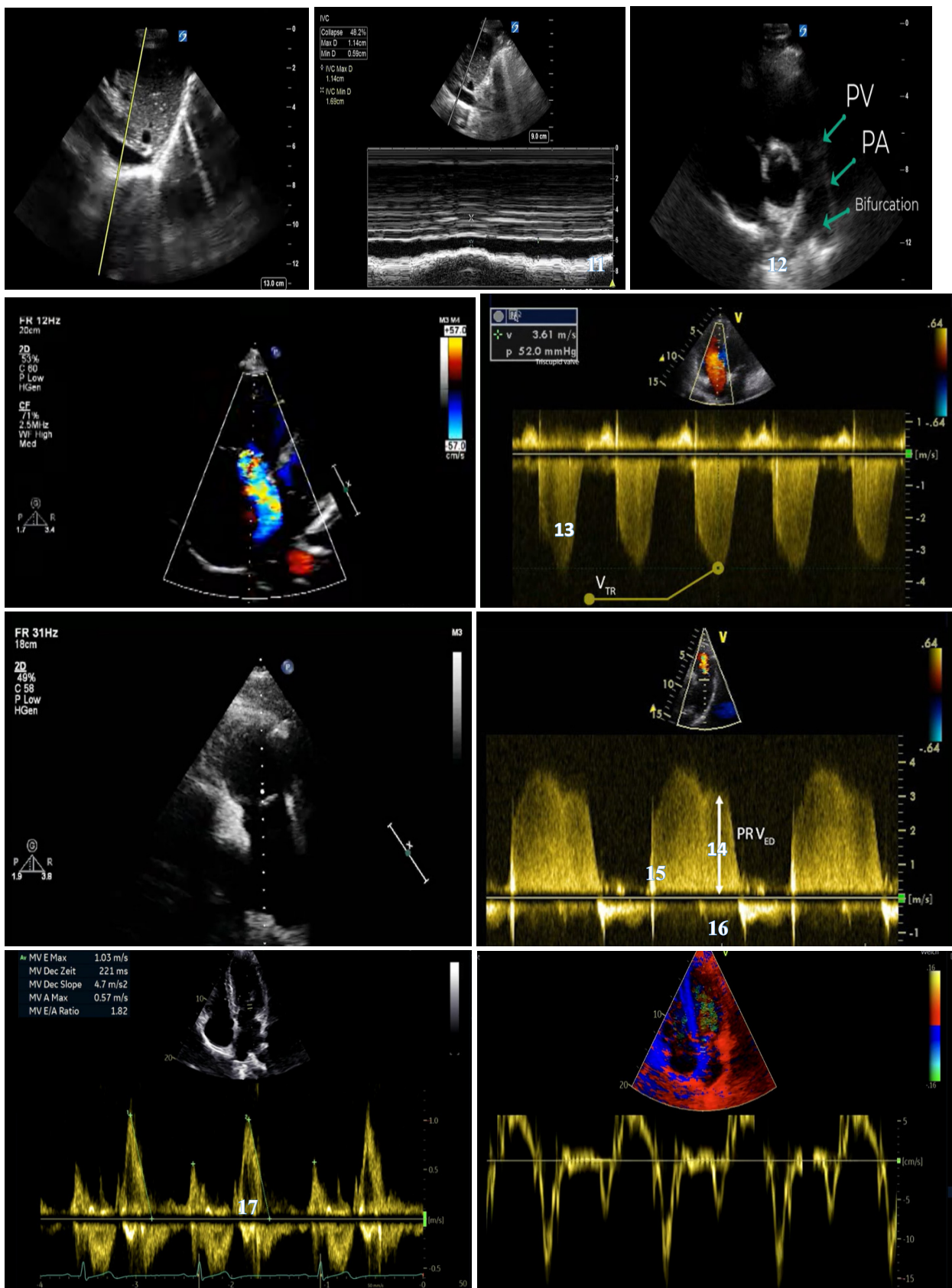


Fig. Illustration of echocardiographic measurements; (1) Measurement of RV basal diameter, (2) Measurement of RV mid-diameter, (3) Measurement of RV longitudinal diameter, (4) Measurement of right ventricular outflow tract diameter, (5) Measurement of RV free wall thickness, (6) Measurement of right atrial diameters, (7) Measurement of RV end-diastolic area (RVEDA), (8) Measurement of RV end-systolic area (RVESA), (9) Measurement of TAPSE, (10) Visualization of the inferior vena cava, (11) Measurement of maximum and minimum inferior vena cava diameters, (12) Measure-

ment of pulmonary artery diameter, (13) Color Doppler visualization of tricuspid regurgitation, (14) Measurement of tricuspid regurgitation using CW and determination of the numerical value for TR Vmax, (15) Detection of pulmonary regurgitation, (16) Measurement of pulmonary regurgitation (PR Vmax), (17) Measurement and display of E/A ratio using PWD, (18) Measurement of e' using TDI.

Statistical Processing

When analyzing the data, the descriptive statistical model will be used for gender, age and distribution of patients with detected RVD in both studied groups. For each of the obtained values from the measurements, the mean value and standard deviation will be derived, and for the parameters with a normal distribution, the Student's T test will be used. The Mann Whitney U test will be used with the obtained values with deviations from the normal distribution. To determine the existence of the need for mechanical ventilation with the development of right ventricular dysfunction based on the definition mentioned above, the Chi square test will be used. The overall prevalence of RVD in all patients included in the study, as well as the RVD prevalence in one group versus the other, will be determined. Determination of differences in parameters used during mechanical ventilation in patients who developed RVD versus those who did not develop RVD will be done using the Mann Whitney U test. Correlation between variables will be evaluated with the Spearman Test, while identification of independent risk factor for development of RVD will be conducted by using a multivariate regression analysis. The mortality and survival rates will be calculated and expressed graphically with the Kaplan Meyer curve. Multivariable logistic regression analysis will be used for identifying possible nondependent predictors for development of RVD in all patients included in the study. Linear regression model for mechanical ventilation settings will be performed for patients exposed to mechanical ventilation in order to identify their possible relationship with RVD. The calculations of the confidence interval (CI-confidence interval) will be performed at a value of 95%, and the values for $p < 0.05$ will be considered statistically significant, while the values for $p < 0.01$ will be considered highly significant.

Limitations

The subjectivity of the physician performing the exam may be a potential limitation in conducting this study, although well experienced and trained echocardiographer performing the examination is a must in order to avoid measurement errors. Inclusion of small number of patients could also be a possible limitation related to the statistical significance of the measured and calculated variables.

Further Possibilities and Applications

This article provides a detailed explanation on the usage and importance of the study protocol explanation, already developed within a PhD thesis. Its publishing is intended to make this protocol available to other researchers who can use it in their practice, or its modulation in further research in the area of the Intensive Care. We recommend that the application of this study protocol in further research is not reserved only to polytraumatized patients, but in many other different cohorts of critically ill patients receiving mechanical ventilation.

Declarations

Ethics approval and consent to participate: Conduction of this study was approved by the Ethical

Committee for Human Research of the Faculty of Medicine in Skopje, at University of SS. Cyril and Methodius – Skopje on 1 February 2023, with approval number 03-300/3.

For the publication of this article, written informed consent was obtained from the patients included in the study until present moment, as well as accompanying data and images. Signing a written informed consent is strongly advised in further inclusion of patients in ongoing research when following this study protocol.

Availability of data and materials: All data are available from the corresponding author upon reasonable request.

Conflict of interest: The authors declare no conflict of interest.

Funding: This research received no external funding.

Authors contributions: All authors have contributed in the design of the study, whereas author A has thoroughly researched existing literature.

Use of Artificial Intelligence (AI) tools: No AI tools were used in the preparation of this manuscript.

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A COMBINED REGIONAL ANESTHESIA-BASED OPIOID-SPARING APPROACH FOR THYMECTOMY IN A PATIENT WITH MYASTHENIA GRAVIS: A CASE REPORT

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Abstract

Introduction: Anesthesia for patients with Myasthenia Gravis requires carefully tailored anesthetic strategy, to minimize the risk of potentially fatal postoperative respiratory failure. A novel regional technique, the superficial parasternal intercostal plane block provides a safe and effective adjunct to combined general anesthesia, which can help reduce perioperative complications.

Case presentation: We report a case of successful anesthetic treatment of a 20-year-old female with Myasthenia Gravis that underwent thymectomy with mid-chest skin incision and sternotomy. The operation was performed under a combined general anesthesia protocol that anticipated strict avoidance of benzodiazepines and muscle relaxants with a decrease in the total dose of opioids. The patient was induced with propofol, fentanyl (50mcg), and remifentanyl infusion. Sevoflurane and low-dose remifentanyl infusion provided adequate hypnosis and sufficient relaxation during the operation. After the endotracheal intubation, we performed a modified bilateral superficial parasternal intercostal plane block, which, in combination with a low-dose remifentanyl infusion, provided optimal analgesia that persisted throughout the postoperative period. The patient was extubated in the operating room and resumed spontaneous breathing without any respiratory complications. Postoperatively, according to the Visual Analog Scale at 4 time points (T₁ – after the operation, T₂ – 6 hours, T₃ – 12 hours, and T₄ – 24 hours), the patient reported minimal or no pain.

Conclusion: The implementation of a regional technique in this case facilitated multimodal analgesia, reduced the overall opioid requirement, and contributed to faster patient recovery. This case highlights the importance of meticulous, individualized planning tailored to the patient's needs in order to achieve favorable outcomes.

Keywords: *Myasthenia gravis; sternotomy; superficial parasternal block.*

Introduction

Myasthenia Gravis (MG) is an autoimmune disorder characterized by skeletal muscle weakness caused by destruction or inactivation of the postsynaptic acetylcholine receptors at the neuromuscular junction. Patients undergoing long-term pharmacological treatment are usually in a steady state and can experience relatively long symptom-free periods. However, in some clinical settings, relapses of MG can be resistant to pharmacological treatment, and patients can experience progression of symptoms despite regular therapy. In this clinical scenario, thymectomy is a recognized treatment option that can lead to long-term symptom improvement, reduced medication requirements, and potential remission, both in patients with thymoma and in those without thymic enlargement (1).

When a patient with MG presents for thymectomy or even for an unrelated surgical procedure, an individual anesthesia plan must be created. The anesthetic management of MG focuses on minimizing the risk of respiratory depression and avoiding exacerbation of the muscle weakness. Benzodiazepines are traditionally described as the biggest potential risk for this patient group. However, the detrimental potential of muscle relaxants and large doses of opioids mustn't be overlooked. Clinical experience, as well as available literature data, are the main guides, with key strategies focused on: regional anesthesia, minimizing the use of respiratory depressants, and avoiding neuromuscular blocking agents (2).

The preoperative evaluation and optimization of their pharmacologic treatment are very important first steps in the management of these patients. A neurology consultation is an essential component of the preoperative assessment and that provides a basis for the postoperative follow-up. The MGFA Clinical Classification is a clinical score accredited worldwide and is used to assess the severity of MG based on muscle weakness patterns and functional impact (3). Thymectomy that involves a mid-chest skin incision and sternotomy is a seriously invasive and painful operation that causes significant tissue destruction and subsequent inflammatory and neuroendocrine response. Thoracic epidural analgesia has historically been considered the gold standard in surgeries involving the thoracic wall. However, recently, regional anesthesia techniques that target the intercostal nerves have gained increasing attention among anesthesiologists worldwide.

The superficial parasternal intercostal plane block (SPIP), which was our technique of choice in this case, is an ultrasound-guided regional anesthesia technique that provides analgesia for thoracic and upper abdominal surgery. The local anesthetic is injected at multiple sites, to target each of the intercostal nerves innervating the dermatomes to be anesthetized. This technique deposits local anesthetic (LA) in a plane between the pectoralis major muscle and external intercostal membrane, targeting the anterior cutaneous branches of Th₂–Th₆. Compared with deep parasternal blocks, in which LA is injected in a fascial plane beneath the intercostal muscles, SPIP is considered a much safer technique because the risk of pneumothorax and vascular injury is significantly lower (4). In our case, we performed a modification of SPIP with additional injection of LA in a plane under the periosteum of the sternum until an ultrasound-visible spread of LA was achieved. This modification was done with the purpose of achieving complete surgical analgesia during sternotomy and thymectomy. Contraindications for SPIP include clinically significant coagulopathy, local infection, or patient refusal.

Case Presentation

We report a case of a 20-year-old female with Myasthenia Gravis (MG) who presented for a

thymectomy because of recent clinical deterioration.

The patient was diagnosed with MG 6 years ago, has since received pharmacological treatment, with regular follow-up by her neurologist. Since December of last year, she has experienced alternating periods of exacerbation and improvement, with symptoms that included difficulty in speaking, nasal speech, difficulty in swallowing, and, more recently, weakness in both arms and occasionally both legs. According to the MGFA clinical classification, our patient was classified as Class IIa (symptoms predominantly in limbs and axial muscles that may include mild oropharyngeal involvement). Patients at this stage of the disease are considered to be at moderate to severe risk of postoperative respiratory complications. (3) She reported a miscarriage at 9 weeks of pregnancy 1 year earlier and had no other relevant medical history.

Her clinical worsening 3 months prior to surgery was pharmacologically treated with prednisolone, azathioprine, and pyridostigmine (Mestinon[®]), but the treatment was unsuccessful, prompting the indication for thymectomy. Preoperative serologic tests detected autoimmune activity with both AChR (0.46 nmol/L) and MuSK (0.2 nmol/L) antibodies. At admission, the patient presented with ptosis of both eyelids, difficulty in speaking and swallowing, and weakness in both arms, mostly in her shoulders. She denied experiencing any respiratory symptoms such as difficulty breathing and coughing. The laboratory analysis and the hemostasis tests were within the reference range. The CT scan of her thorax showed a small mass (2-3cm) in the upper mediastinum with radiological characteristics of normal gland tissue or adipose tissue.

Our plan was to use a combined anesthesia approach focused on avoiding all agents that could contribute to the progression of the patient's disease, while providing adequate intra- and postoperative analgesia. Preoperative premedication with benzodiazepines was omitted. The patient was induced with propofol (1.5mg/kg) and 50mcg of fentanyl, which provided optimal intubation conditions, and she was intubated with a size 7 endotracheal tube. Throughout the entire procedure, hypnosis was provided with sevoflurane (1vol%) and continuous remifentanyl infusion (0.15-0.25mcg/kg/min). Muscle relaxants were not used during the operation.

After induction and intubation, we performed an ultrasound-guided modified superficial parasternal intercostal plane block (SPIP), using a combination of lidocaine (30mg) and bupivacaine (75mg). According to her body weight (74 kg) and body mass index (28), the total administered doses of LA were in the safe therapeutic range for RA and significantly lower than the maximal recommended doses for lidocaine (30mg used versus maximal dose 3mg/kgBW) and bupivacaine (75mg used versus maximal dose 2mg/kgBW). Using a linear ultrasound probe (5-15 MHz) and a 100mm ultrasound needle, under strict aseptic technique, SPIP was performed with several injections in 4 adjacent intercostal sites on both sides of the sternum. LA was injected in a plane between the pectoralis major muscle and the external intercostal membrane. (picture 1) In order to achieve complete surgical analgesia of the sternum and the anterior chest wall, we decided to modify SPIP by adding a separate superficial injection of lidocaine and bupivacaine in the plane deep to the periosteum of the sternum. This ultrasound-guided injection was performed in the middle third of the sternum, with visible spread of the LA beneath the periosteum in both cranial and caudal directions.

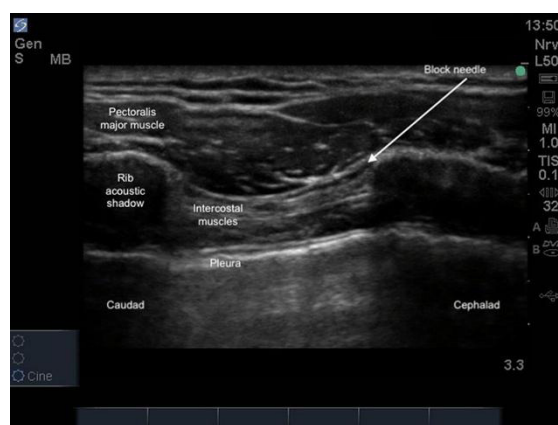


Image 1: Ultrasound view of the needle position during SPIS

The patient also received ceftriaxone, methylprednisolone (80mg), and famotidine (20mg) intraoperatively. Before emergence from general anesthesia, a 100ml Comboval® infusion was administered, containing 1.0 g of paracetamol and 300mg of ibuprofen. The procedure lasted a total of 2h45min and was uneventful. Continuous monitoring included ECG, SaO₂, non-invasive blood pressure, and end-tidal CO₂. The patient was completely hemodynamically and respiratory-wise stable, with variations in blood pressure and heart rate of less than 20% from baseline at all times during the procedure. The patient was successfully extubated in the operating room and resumed sufficient spontaneous breathing without any respiratory complications. After the surgery, the patient was transferred to the post-anesthesia care unit (PACU) and later to the surgery ward of the UC of Thoracic and Vascular Surgery until her discharge from hospital.

Her postoperative pain intensity was subjectively graded using the Visual Analog Scale (VAS 0/10 – with 0 being no pain and 10 being the worst pain possible) at 4 timepoints: (T₁) immediately after emergence from anesthesia, (T₂) after 6 hours, (T₃) after 12 hours and (T₄) after 24 hours. The results were: T₁ – 2-3; T₂ – 1-2; T₃ – 0-1; T₄ – 0. On the day of surgery and the 1st postoperative day, rescue analgesia with Paracetamol 1.0gr was required only for treatment of mild pain. The day after surgery, arterial blood gas analysis showed satisfactory respiratory function: pO₂ 97.4mmHg, pCO₂ 35.0 mmHg, SaO₂ 96.8%, pH 7.45. The clinical examination, as well as the blood gas analysis, indicated solid respiratory function and excellent recovery progress with minimal to no pain.

Discussion

The treatment of postoperative pain is a serious challenge, especially following thoracic surgery and sternotomy, known to be extremely painful procedures. Inadequate postoperative analgesia is associated with insufficient mobility, atelectasis, impaired pulmonary function and prolonged hospital stays, ultimately compromising the overall quality of recovery. Modern literature highlights the impact of prolonged pain on inflammation and the activation of the neuroendocrine cascade, leading to a complex stress response that is detrimental to the immune system mechanisms (5). For these reasons, inadequate pain treatment is considered a silent propagator of complications in the postoperative period.

A nationwide matched cohort study by Yi-Wen Chang et al, showed that surgical patients with MG

are at a higher risks of postoperative pneumonia, septicemia and postoperative bleeding compared to surgical patients without MG (6). In their clinical study, Dost et al. reported that acute postoperative pain is a well-recognized risk factor for the development of chronic postsurgical pain, which can affect up to 20–60% of patients undergoing thoracic procedures (7). Administration of high-dose opioids is not ideal for any patient due to side effects, such as: nausea, vomiting, constipation, urinary difficulty, respiratory depression, sedation, possible persistent postsurgical pain, and drug dependency. All of these are even more concerning in patients with MG. Therefore, in recent years regional anesthesia techniques have become a valuable addition to balanced multimodal analgesia protocols. In this case, the regional anesthesia technique of choice was the superficial parasternal intercostal plane block (SPIP). This technique aims to anesthetize the anterior branches of the Th₂-Th₆ intercostal nerves, providing effective analgesia during general anesthesia for sternotomy. This block was originally described by de la Torre in 2014 as a regional anesthesia technique for patients undergoing breast surgery. Its wider use in patients primarily undergoing sternotomy in cardiac surgery has been recently proposed by Kumar et al., as well as in other sternotomy cases (8,9). Since the sternal periosteum is highly innervated and therefore highly sensitive to pain, the injection of the LA beneath the periosteum, in addition to the SPIP, provides a more effective and targeted intraoperative and postoperative analgesia. The intra-periosteal application of LA, originally described by Duncan et al. in 2002, is a recognized treatment for trauma patients with sternal fractures, but is not frequently used in elective surgery requiring a sternotomy. In our case, a single-shot injection provided sufficient surgical analgesia, rather than a continuous infusion via a periosteal-placed catheter, as described by Duncan et al. (10). The strategy behind multimodal analgesia is to combine different classes of medications and techniques that provide analgesia relying on different mechanisms, with the goal of optimizing pain control and minimizing the risk of potential side effects. The net result of the combined anesthesia protocol in our patient was a reduction in total opioid requirement, and minimal or no postoperative pain with only minimal use of rescue anesthesia consisting of paracetamol and ibuprofen.

While multimodal analgesia planning is important for every patient, surgical patients with MG are more vulnerable and require a carefully planned and individualized protocol. The rapid onset, short-term action, and swift awakening make remifentanyl the preferred opioid for this group of patients. This modified regional anesthesia technique, together with the administered intravenous drugs, allowed for an optimal recovery of the patient.

Conclusion

Although each patient presents a unique challenge for an anesthesiologist, the successful management of patients with Myasthenia Gravis requires a multidisciplinary, multimodal approach, a profound understanding of the disease pathophysiology, and an individually tailored strategy. The contemporary practice of anesthesia offers numerous modalities and techniques that allow us to follow the key principles of anesthetic management for patients with MG: avoiding exacerbation of muscle weakness and preserving respiratory function. In our patient with symptomatic MG, a modified bilateral SPIP as an addition to the general anesthesia allowed for a painless and uneventful recovery.

Although the initial findings are promising, one major limitation of this report was that it assesses the clinical outcome of treatment in a single patient. Additional research and randomized clinical trials are necessary to establish the true significance of this technique in the treatment of different patient groups.

Declarations

Ethics approval and consent to participate: All data are available from the corresponding author upon reasonable request.

Informed consent: For the publication of this case report, a written informed consent was obtained from the patient, along with accompanying data and images.

Conflict of interest: The authors declare no conflict of interest.

Funding: This research received no external funding.

Author's contributions: Author A and Author B contributed in patient management and data collection; Author C contributed in the patient's postoperative follow-up and data collection; Author D did the literature review and supervision, while Author F contributed in data processing and writing; Author E was responsible for the surgical treatment of the patient and the follow-up in the postoperative treatment at the surgical ward.

Artificial Intelligence (AI) statement: No AI tools were used in the preparation of this manuscript.

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ACUTE STANFORD TYPE A AORTIC DISSECTION PRESENTING WITH RESPIRATORY SYMPTOMS AS THE INITIAL MANIFESTATION OF SUSPECTED MARFAN SYNDROME: CASE REPORT

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Abstract

Introduction: Acute Stanford type A aortic dissection is a life-threatening emergency that requires immediate diagnosis and surgical intervention. While the classic presentation involves severe chest or back pain, recognition may be delayed in patients with atypical symptoms, particularly those with underlying connective tissue disorders such as Marfan syndrome.

Case Presentation: A 46-year-old man (height 190 cm) with no prior diagnosis of connective tissue disease presented with a three-day history of fever, cough, and mild chest discomfort, without severe chest, back, or abdominal pain. Physical examination revealed a Marfanoid habitus, and the family history was notable for aortic dissection in several first-degree relatives. Computed tomography angiography of the aorta identified an acute Stanford type A (DeBakey I) dissection originating at the aortic root and extending through the ascending aorta, aortic arch, and descending thoracic aorta, with propagation toward the iliac arteries. Transthoracic echocardiography confirmed the diagnosis by revealing a markedly dilated aortic root (66–68 mm), an intimal flap at the right coronary cusp, and severe aortic regurgitation. The patient underwent urgent surgical repair using a Bentall procedure. The postoperative course was complicated by significant bleeding, requiring surgical re-exploration. Following this intervention, recovery was uneventful. The overall clinical presentation and perioperative findings were most consistent with an underlying diagnosis of Marfan syndrome.

Conclusion: This case underscores the importance of considering aortic dissection in patients with a Marfanoid phenotype and positive family history, even when typical symptoms are absent. Early diagnosis and surgical intervention are critical for improving survival in this high-risk population.

Keywords: Aortic dissection; Bentall procedure; Marfan syndrome.

Introduction

Acute type A aortic dissection (ATAAD) is a life-threatening cardiovascular emergency involving the ascending aorta that requires prompt diagnosis and immediate surgical intervention (1,2). Without timely surgical treatment, early mortality increases by approximately 1% to 2% per hour during the first 24 hours, and nearly half of untreated patients die within one week (1). Diagnosis becomes particularly challenging when patients lack the classic symptoms of sudden, severe, tearing chest or back

pain and instead present with nonspecific complaints, which can delay definitive treatment (2–4).

In younger adults, the presence of marfanoid features combined with a strong family history of aortic dissection should raise suspicion for both ATAAD and an underlying heritable thoracic aortic disorder (1,5). However, Marfan syndrome cannot be diagnosed solely on the basis of these features; a comprehensive clinical evaluation using established criteria and, when appropriate, molecular genetic testing is required (5,6). This report describes an extensive ATAAD in a young adult with marfanoid features and a significant family history who presented with fever, cough, dyspnea, and only mild chest discomfort. This atypical, minimally painful presentation initially suggested a predominantly respiratory illness. This case highlights the necessity of considering acute aortic pathology in high-risk patients even when characteristic pain is absent, which can lead to earlier diagnosis and treatment.

Case Presentation

A 46-year-old male patient was admitted to the hospital with a three-day history of fever, cough, dyspnea, and mild chest discomfort. He denied any sudden or severe chest, back, or abdominal pain. His medical history included hypertension, hyperlipidemia, hyperthyroidism, and active tobacco use. Importantly, he had not previously been diagnosed with Marfan syndrome or other connective tissue disorders.

On admission, the patient was hemodynamically stable, with a blood pressure of 104/70 mmHg in the right arm and 115/80 mmHg in the left arm, and a heart rate of 90 beats per minute in sinus rhythm. He was 190 cm tall and weighed 80 kg, exhibiting features suggestive of a marfanoid habitus. Furthermore, the patient reported a family history of aortic dissection affecting his father, mother, and sister; however, the ages of these relatives at the time of dissection were not documented.



Figure 1. Chest radiograph demonstrating enlargement of the aortic arch silhouette (arrow), with no focal pulmonary consolidation.

The initial presentation suggested a respiratory illness, with pneumonia and viral respiratory infection considered in the differential diagnosis. However, chest radiography revealed no focal pulmonary consolidation but demonstrated enlargement of the aortic silhouette (Figure 1). Based on this finding, along with marfanoid features and a significant family history, computed tomography angiography (CTA) of the aorta was performed. CTA revealed a dissection extending from the aortic root through the ascending aorta, aortic arch, descending thoracic aorta, and abdominal aorta to the aortic bifurca-

tion, with further extension into the right iliac artery (Figure 2). These findings were consistent with a Stanford type A, DeBakey type I aortic dissection.

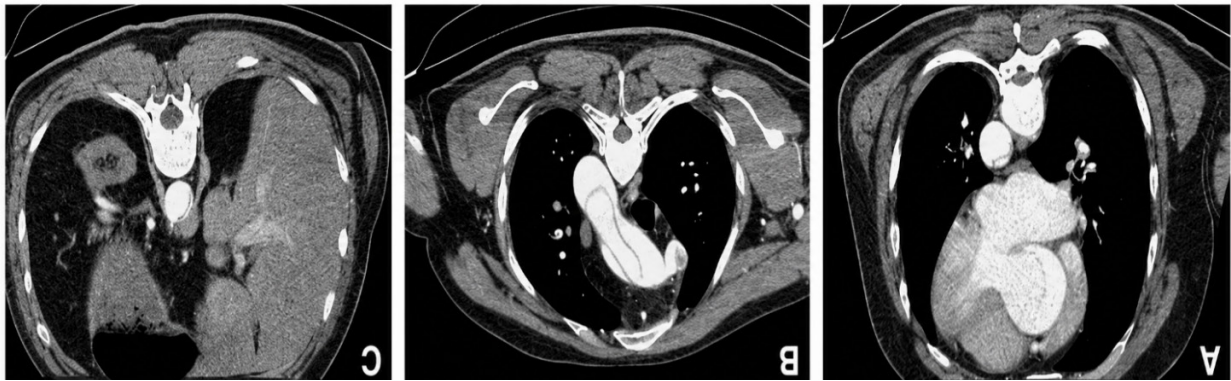


Figure 2. CTA images showing an extensive Stanford type A, DeBakey type I aortic dissection:

(A) involvement of the aortic root; (B) extension through the ascending aorta and aortic arch;

(C) propagation into the abdominal aorta.

Transthoracic echocardiography demonstrated marked dilatation of the proximal aorta and a mobile intimal flap at the level of the right coronary cusp (Figure 3A). The aortic root measured 66 to 68 mm at the sinuses of Valsalva and sinotubular junction, while the ascending aorta measured 66 mm. Severe eccentric aortic regurgitation was present, with a vena contracta width of 0.6 cm (Figure 3B). Despite these findings, left ventricular systolic function was preserved, with an ejection fraction of 62%.

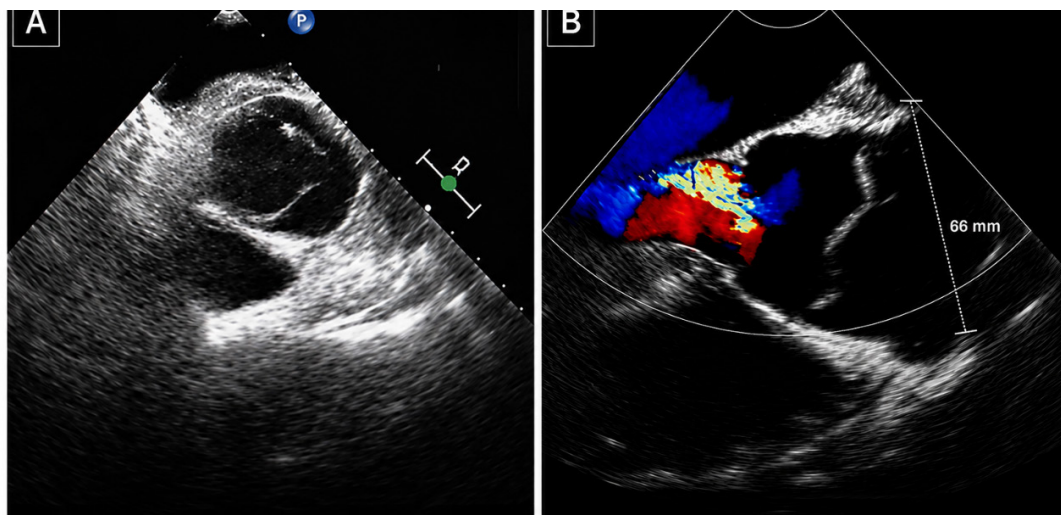


Figure 3. Transthoracic echocardiographic images demonstrating (A) an intimal flap at the level of the right coronary cusp and (B) marked aortic root dilatation measuring 66 mm, with color Doppler evidence of severe eccentric aortic regurgitation.

The patient subsequently underwent emergency surgical repair. General anesthesia was induced with

etomidate, fentanyl, and rocuronium and maintained with sevoflurane until the initiation of cardiopulmonary bypass, after which anesthesia was maintained with a propofol infusion. Central venous and large-bore venous access were established, alongside invasive femoral arterial pressure monitoring. Cerebral oxygenation was continuously monitored using near-infrared spectroscopy (NIRS), and hemostatic management was guided by rotational thromboelastometry (ROTEM). Cardiopulmonary bypass was established through ascending aortic cannulation and right atrial cannulation with a two-stage venous cannula. A Bentall procedure was performed using a CarboMedics mechanical composite valved conduit comprising a 27-mm mechanical valve and a 30-mm vascular graft (Figure 4). On the first postoperative day, excessive surgical drain output necessitated re-exploration to identify bleeding and surgical hemostasis.

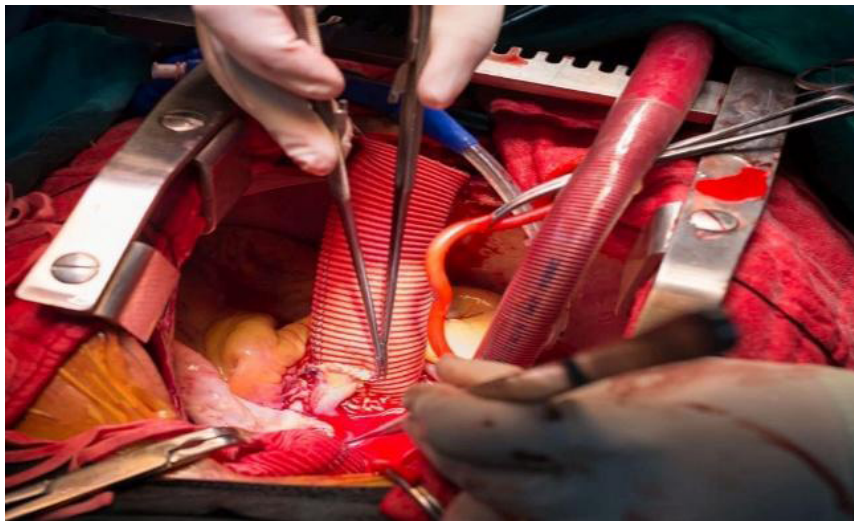


Figure 4. Intraoperative image of aortic root replacement with a mechanical composite valved conduit during the Bentall procedure.

Postoperatively, the patient required temporary mechanical ventilation and vasoactive support but remained in sinus rhythm. He was successfully weaned from mechanical ventilation, and vasoactive therapy was gradually reduced and discontinued. Early mobilization and physical rehabilitation were initiated, and the patient was discharged in stable condition on postoperative day 5 with a prescription for lifelong oral anticoagulation (acenocoumarol) due to the mechanical aortic valve prosthesis.

At follow-up assessments conducted at one week, one month, and six months after surgery, the patient remained clinically stable. Further evaluation was scheduled at one year, followed by annual cardiology assessments and lifelong imaging surveillance of the residual aorta.

The presence of marfanoid features, marked aortic root dilatation, and aortic dissection in three first-degree relatives raised strong suspicion for an underlying heritable thoracic aortic disorder. However, the systemic manifestations required for assessment under the revised Ghent criteria had not been comprehensively documented, so a valid systemic score could not be calculated. Additionally, ophthalmologic evaluation, genetic counseling, and molecular genetic testing had not yet been performed; therefore, Marfan syndrome remained suspected but unconfirmed.

Discussion

Acute type A aortic dissection is a surgical emergency due to the risk of rapid progression to life-threatening complications, including aortic rupture, cardiac tamponade, acute aortic regurgitation, coronary malperfusion, stroke, and organ ischemia (1,2). Current European guidelines recommend immediate surgical intervention upon diagnosis (1), regardless of apparent hemodynamic stability, as significant disease may be present even in stable patients (1,3). In the present case, pronounced proximal aortic dilatation, severe aortic regurgitation, and a dissection extending into the abdominal aorta and right iliac artery signified advanced disease despite initial clinical stability.

Acute aortic dissection typically presents with abrupt, severe chest or back pain (2); however, the absence of typical pain does not exclude the diagnosis. In a population-based study by Smedberg et al., 18% of patients with ATAAD presented without pain, and painless presentation was independently associated with increased 30-day mortality in the overall cohort (4). Data from the International Registry of Acute Aortic Dissection (IRAD) further indicate that painless dissection may instead manifest as syncope, heart failure, or stroke, potentially delaying recognition of the underlying aortic emergency (3). In the present case, the patient experienced only mild chest discomfort and did not report the abrupt, severe pain typically associated with aortic dissection. The predominance of respiratory symptoms and fever initially indicated a possible respiratory or infectious illness. However, the etiology of these symptoms remained unclear, and the possibility of a concurrent respiratory infection could not be excluded. Therefore, these symptoms cannot be definitively attributed to the dissection. Although enlargement of the aortic silhouette on chest radiography was not diagnostic in isolation (1), this finding, together with the patient's marfanoid features and strong family history of aortic dissection, prompted definitive cross-sectional imaging.

CTA is the preferred first-line imaging modality for most hemodynamically stable patients with suspected acute aortic dissection, as it is rapid, widely accessible, and enables comprehensive evaluation of the entire aorta, including the delineation of true and false lumina, identification of the entry tear, assessment of branch-vessel involvement, and detection of major complications (1,2). In the present case, CTA played a pivotal role in establishing the diagnosis, revealing a DeBakey type I dissection extending from the aortic root to the aortic bifurcation and into the right iliac artery. Transthoracic echocardiography provided complementary information by visualizing the proximal intimal flap, quantifying aortic root and ascending aortic dilatation, demonstrating severe eccentric aortic regurgitation, and assessing left ventricular systolic function. The combined use of CTA and echocardiography was therefore essential for detailed anatomical characterization and precise surgical planning.

The patient underwent emergency surgical repair, as the dissection involved the ascending aorta (1,2). The presence of a markedly aneurysmal aortic root measuring 66–68 mm, together with severe aortic regurgitation, provided a clear anatomical rationale for composite aortic root replacement (1). In this case, a Bentall procedure was performed, addressing both the diseased aortic root and the aortic valve in a single operation. Although valve-sparing root replacement may be considered in selected patients, particularly when the valve cusps are suitable for repair and the procedure is performed by an experienced aortic surgical team (1), the substantial root dilatation and severity of aortic regurgitation in this emergency context favored composite root replacement. The implantation of a mechanical valved conduit consequently necessitated lifelong anticoagulation with acenocoumarol (Sintrom).

The patient's relatively young age, marfanoid features, marked aortic root dilatation, and a family

history of aortic dissection in three first-degree relatives strongly suggested an underlying heritable thoracic aortic disorder (1,5). However, neither the presence of marfanoid habitus nor a family history of aortic dissection is, on its own, sufficient to diagnose Marfan syndrome (5,6). According to the revised Ghent criteria, a diagnosis of Marfan syndrome can be established based on specific combinations of aortic root dilatation or dissection, and additional features such as ectopia lentis, a pathogenic FBN1 mutation, a systemic score of ≥ 7 , or a family history of confirmed Marfan syndrome (5,6). In this patient, the lack of comprehensive documentation of systemic features and the absence of both ophthalmologic evaluation and molecular genetic testing precluded a definitive diagnosis, leaving Marfan syndrome suspected but unconfirmed. Accordingly, comprehensive phenotypic assessment, ophthalmological examination, genetic counseling, and molecular testing are recommended to clarify the diagnosis and guide family risk assessment. First-degree relatives should undergo screening aortic imaging, with cascade genetic testing if a pathogenic or likely pathogenic variant is identified (1,5).

The dissection extended beyond the surgically replaced segment, leaving the residual aorta at ongoing risk of progressive dilatation, aneurysmal degeneration, and potentially requiring future reintervention. Therefore, strict blood pressure control and lifelong cross-sectional imaging surveillance of the entire aorta are essential components of long-term management, regardless of apparent clinical stability (1).

Conclusion

This case illustrates that acute type A aortic dissection may present atypically in relatively young patients with features suggesting heritable aortic disease, even in the absence of characteristic severe pain. Early identification of subtle radiographic findings, together with consideration of phenotypic and family history, is critical for timely diagnosis and intervention. Clinicians should maintain a high level of suspicion in at-risk individuals and ensure ongoing assessment of both patients and their first-degree relatives to improve clinical outcomes.

Declarations

Ethics approval and consent to participate: A formal approval of the Ethics Committee was not required for this study.

Informed consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of interest: The authors declare no conflict of interest.

Funding: No external funding was received.

Author contribution statement: All authors contributed to the conception of the case report, data collection, manuscript preparation, and approved the final version of the manuscript.

Artificial Intelligence (AI) statement: AI tools were used for language editing. The authors take full responsibility for the content.

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SPONTANEOUS RESOLUTION OF A LARGE NEONATAL ABDOMINAL LYMPHATIC MALFORMATION MANAGED CONSERVATIVELY: A CASE REPORT

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Abstract

Introduction: Abdominal lymphatic malformations are rare benign malformations of the lymphatic system, most commonly diagnosed during childhood, whereas prenatal and neonatal diagnosis are exceedingly rare. These lesions can enlarge and cause significant morbidity due to compression of adjacent organs. Therefore, surgical excision is traditionally considered the treatment of choice.

Objective: To present a case of a neonate with a large abdominal lymphatic malformation that was managed conservatively with a favorable outcome.

Case presentation: We present the case of a male moderate preterm neonate with apparent colonic dilatation on fetal ultrasonography, raising suspicion of intestinal atresia. After birth, the infant developed abdominal distension and respiratory distress. Radiological evaluation revealed a cystic lesion located in the left hemiabdomen and left retroperitoneal space, consistent with a large neonatal abdominal lymphatic malformation, measuring 55 × 65 × 133 mm at its maximum dimensions. A multidisciplinary board evaluated the risks of surgical intervention versus conservative observational management. At 16 months of age, complete spontaneous resolution of the lesion was documented.

Conclusion: This rare outcome suggests that not all abdominal lymphatic malformations in the neonatal period require surgical treatment. In carefully selected, clinically stable neonates, an initial strategy of watchful waiting supported by strict clinical and ultrasonographic surveillance is a safe alternative to immediate surgery or sclerotherapy. Establishing clear multidisciplinary intervention criteria remains essential to ensure patient safety during conservative observation.

Keywords: conservative approach; lymphatic malformation; preterm neonate.

Introduction

Abdominal lymphatic malformations are rare benign malformations of the lymphatic system, most commonly diagnosed during childhood, whereas prenatal and neonatal presentation are exceedingly rare (1). These lesions result from abnormal embryologic development of the lymphatic system, spe-

cifically from failed communication between lymphatic ducts and the venous system (2). Although lymphangiomas can occur throughout the body, approximately 95% are located in the neck and axillary regions, whereas intra-abdominal localization accounts for only 4–5% of cases (3). Mesenteric, omental, and retroperitoneal involvement is particularly uncommon (1, 7).

These lesions can enlarge and cause significant morbidity due to compression of adjacent organs, intestinal obstruction, volvulus, hemorrhage, infection, or rupture. Therefore, surgical excision is traditionally considered the treatment of choice (1). However, emerging evidence suggests that clinically stable neonates without acute abdominal emergencies may undergo spontaneous regression, highlighting the potential role of conservative management.

Objective

To present a case of a neonate with large abdominal lymphatic malformation that was managed conservatively with a favorable outcome.

Case Presentation

We present the case of a moderately preterm male neonate delivered at 32+1 weeks of gestation by cesarean section following a pregnancy complicated by oligohydramnios. Fetal ultrasonography demonstrated apparent colonic dilatation, raising suspicion of intestinal atresia; however, prenatal findings remained inconclusive (Figure 1a). Birth weight was 1915 g, with Apgar scores of 6, 6, and 7 at the 1st, 5th, and 10th minute, respectively.



1a.



1b.

Figure 1a. Transverse sonographic section of the fetal abdomen demonstrating dilated intestinal loops

Figure 1b. Neonatal abdominal radiograph showing soft-tissue opacity suggestive of an intra-abdominal cystic lesion.

Initial resuscitation required positive pressure ventilation via a T-piece resuscitator. Upon transfer to the neonatal intensive care unit, non-invasive respiratory support with continuous positive airway pressure (CPAP) was initiated, and surfactant was administered via the less invasive surfactant administration (LISA) technique due to respiratory distress syndrome. CPAP respiratory support was required until postnatal day 6, followed by high-flow nasal cannula (HFNC) support until postnatal

day 8.

On admission, physical examination revealed abdominal distension and subcostal retractions. The abdomen was soft on palpation, with no palpable localized masses or organomegaly. Meconium was passed within the first 24 hours of life.

Parenteral nutrition was initiated on postnatal day 3 and continued until postnatal day 8. An initial enteral feed trial on postnatal day 4 resulted in transient bilious vomiting, prompting temporary feed cessation and diagnostic workup. Minimal enteral feeding was subsequently and successfully reintroduced on postnatal day 6 using expressed breast milk and preterm formula, with feeds progressively advanced to full oral feedings by postnatal day 12, without recurrence of emesis.

Laboratory findings were unremarkable except for transient hyperbilirubinemia, which was managed with phototherapy. Inflammatory markers remained within normal limits throughout hospitalization.

Given the prenatal suspicion of gastrointestinal pathology and the presence of postnatal abdominal distension with bilious vomiting, further diagnostic evaluation was performed.

Initially, a plain abdominal radiography was performed (Figure 1b). Contrast enema demonstrated a preserved rectosigmoid ratio with no radiographic signs of Hirschsprung disease. Bowel loops were displaced by a large cystic intra-abdominal mass.

Abdominal ultrasound revealed a large multiloculated cystic lesion occupying the left hemiabdomen with displacement of adjacent abdominal structures, highly suggestive of a lymphatic malformation.

Magnetic resonance imaging of the abdomen and pelvis provided precise anatomical delineation, confirming a large multicystic lesion involving the left hemiabdomen and retroperitoneal space, measuring $55 \times 65 \times 133$ mm (Figure 2a-c). The lesion demonstrated low signal intensity on T1-weighted images and high signal intensity on T2-weighted images, with internal septations showing mild post-contrast enhancement. The lesion extended through the left inguinal canal into the left hemiscrotum and caused displacement of adjacent organs, including the left kidney. These characteristic imaging features strongly supported the diagnosis of an extensive abdominal lymphatic malformation.

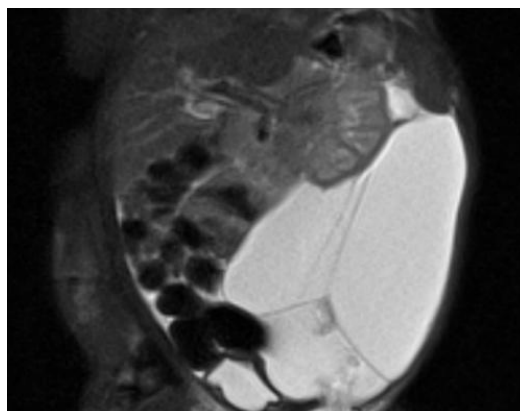


Figure 2a. Sagittal T2-weighted MRI

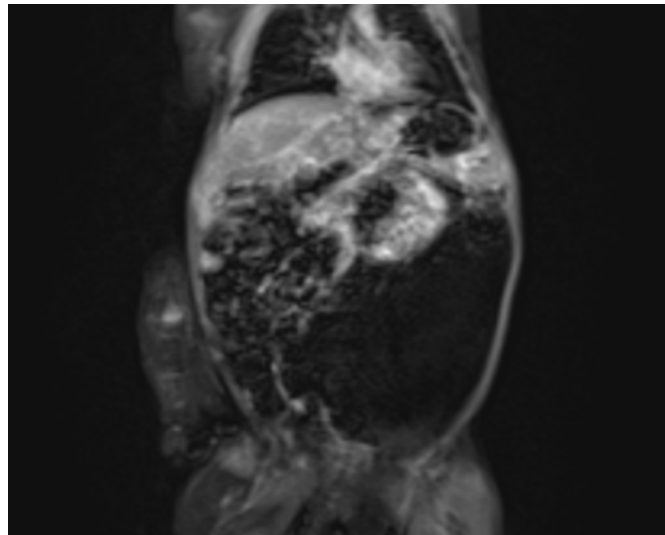


Figure 2b. Axial T2-weighted MRI

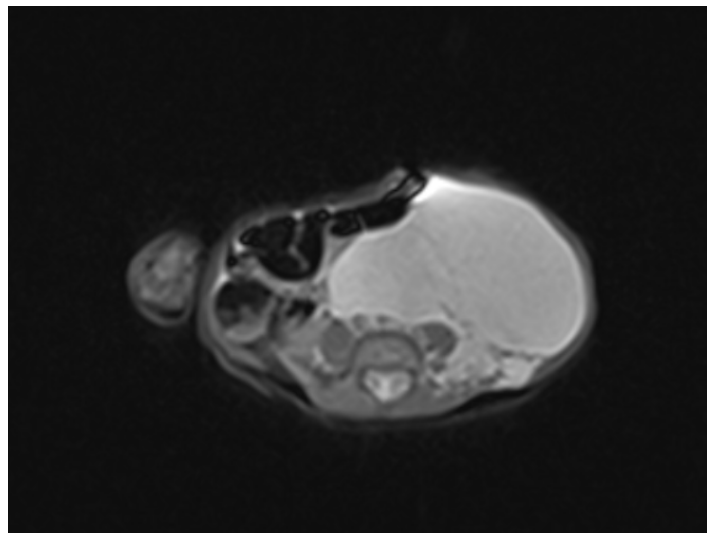


Figure 2c. Coronal T2-weighted MRI

Figure 2. Magnetic resonance imaging of the abdomen and pelvis demonstrating a large multiloculated cystic lesion consistent with abdominal lymphatic malformation. The lesion occupies the left hemiabdomen, displaces adjacent bowel loops and abdominal organs, and extends through the left inguinal canal into the left hemiscrotum.

Echocardiography revealed mild myocardial hypertrophy with preserved cardiac function and persistent fetal shunts. Cranial ultrasonography showed no intracranial abnormalities.

Given that no tissue biopsy, fluid aspiration, or histopathological examination was performed, a working diagnosis of an abdominal lymphatic malformation was established based on multiplanar

MRI criteria.

A multidisciplinary board—comprising neonatologists, pediatric surgeons, and pediatric radiologists—evaluated the risks of surgical intervention (e.g., extensive bowel resection, vascular injury, retroperitoneal trauma) versus conservative observational management. Given that the infant achieved full enteral feeding tolerance, displayed consistent weight gain, maintained normal renal function, and showed no signs of bowel ischemia or acute abdomen, conservative observation was selected. Nonetheless, a strict clinical rescue plan was established with the parents and the surgical team. Immediate surgical intervention was planned if predefined triggers were met (progressive lesion enlargement, recurrent bilious vomiting or clinical signs of intestinal obstruction/volvulus, inability to maintain full enteral nutrition or progressive failure to thrive, acute abdominal distress, renal compromise or inguinoscrotal complications).

Following discharge from the NICU on postnatal day 22, the patient was enrolled in a protocolized outpatient follow-up program consisting of serial pediatric surgical evaluations and standardized abdominal ultrasonography (every three months), with the patient's clinical course summarized in the timeline presented in Figure 3. At 16 months of age, abdominal ultrasonography confirmed complete resolution of the lymphatic malformation. Ongoing clinical surveillance through 24 months of age confirmed no recurrence.

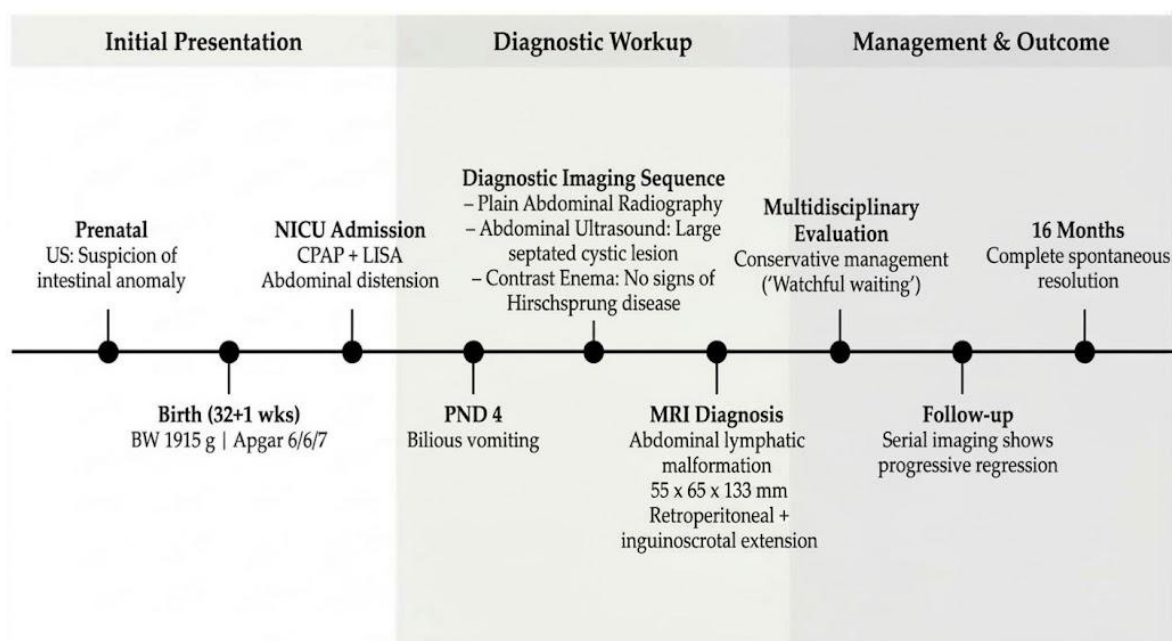


Figure 3. Timeline of the patient's clinical course

Discussion

Due to the rarity of intra-abdominal lymphangiomas, the uncertainty regarding their natural history and biological behavior, and the difficulty in obtaining a preoperative histological diagnosis, the question of whether and when surgery should be performed remains controversial (4). Given that preoperative tissue diagnosis is rarely available and histopathological confirmation was not performed in our patient, classifying such lesions purely as “mesenteric lymphangiomas” based solely on imaging findings may be imprecise, particularly when retroperitoneal and inguinoscrotal structures are simultaneously involved. Therefore, the broader diagnostic umbrella of abdominal lymphatic malforma-

tion more accurately reflects the clinical reality when managed nonoperatively.

Surgical excision is generally considered the standard treatment because of the potential risk of bowel obstruction, volvulus, hemorrhage, infection, rupture, and compression of adjacent structures (1,5). However, several reports have described spontaneous regression of lymphatic malformations, particularly in clinically stable patients without acute complications. Consequently, conservative management with close radiological follow-up has emerged as a potential alternative in carefully selected cases (5). Recent literature also highlights the growing role of minimally invasive and conservative approaches in certain lymphatic malformations, including sclerotherapy and observational management in clinically stable patients (6).

The clinical course of lymphatic malformations is highly variable, ranging from spontaneous regression to progressive enlargement associated with severe complications (8). Therefore, individualized management based on clinical presentation, lesion extent, and patient stability remains essential.

Ultrasonography is an excellent modality for the detection and follow-up of these lesions and is generally preferred for serial monitoring (5,7). Computed tomography and magnetic resonance imaging are valuable diagnostic tools, while MRI provides the most detailed anatomical characterization of lesion extent and its relationship with surrounding structures (5). Differential diagnosis of neonatal cystic intra-abdominal lesions includes duplication cysts, mesothelial cysts, ovarian cysts, meconium pseudocysts, teratomas, and cystic neuroblastoma, making detailed radiological evaluation essential (7).

Our case highlights that even extensive lesions causing anatomical displacement can safely undergo complete spontaneous resolution without intervention. Despite the large size of the lesion and its extensive retroperitoneal and inguinoscrotal extension, the absence of persistent bowel obstruction, hemodynamic instability, progressive lesion enlargement, or clinical deterioration supported a conservative approach. However, the safety of “watchful waiting” critically depends on defining strict clinical stability—characterized by adequate intestinal transit, absence of systemic toxicity, normal renal function, and growth—alongside a predefined surgical rescue plan.

To the best of our knowledge, reports of complete spontaneous resolution of a large neonatal abdominal lymphatic malformation with retroperitoneal and inguinoscrotal extension remain extremely limited in literature.

Conclusion

Complete spontaneous resolution can occur even in extensive neonatal abdominal lymphatic malformations. In carefully selected, clinically stable neonates, an initial strategy of watchful waiting supported by strict clinical and ultrasonographic surveillance is a safe alternative to immediate surgery or sclerotherapy. Establishing clear multidisciplinary intervention criteria remains essential to maintaining patient safety during conservative observation.

Declarations

Ethics approval and consent to participate: A formal approval from the Ethics Committee was not required for this study.

Informed consent: Written informed consent was obtained from the patient's parent.

Conflict of interest: The authors declare no financial or personal conflicts of interest.

Funding: No external funding was received.

Author's contributions: All authors contributed to the conception of the case report, the data collection, the manuscript preparation, and approved the final version of the manuscript.

Acknowledgements: The authors thank the radiology staff of the Institute of Radiology, Faculty of Medicine, Ss. Cyril and Methodius University of Skopje, for their assistance.

Use of Artificial Intelligence (AI) tools: The authors declare that no artificial intelligence tools were used in the preparation of this manuscript.

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PRESENTING THE MACEDONIAN NUCLEAR MEDICINE EXPERIENCE AT THE SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING ANNUAL MEETING 2026

Dear Editor,

I was delighted to attend the SNMMI Annual Meeting 2026, held from May 30 to June 2, 2026, in Los Angeles, USA, organized by the Society of Nuclear Medicine and Molecular Imaging (SNMMI). Attracting nearly 8,000 attendees from across the globe, it is considered as one of the largest international events in the nuclear medicine field.

More than 130 continuing education and scientific sessions highlighted advances and important developments in precision nuclear medicine, such as theranostics, quantification techniques, as well as updates in radiopharmaceutical production. Further opportunities for acquiring insight and knowledge were also offered at the Annual Meeting Science Pavilion, where 1000s of posters were presented and at the exhibition hall, where 250 leading companies and organizations exhibited their work at the meeting. The meeting also received close to 1,500 abstract submissions, representing an increase compared with the previous year and the highest number of submissions since the pre-COVID-19 period (1).

In addition to learning about the latest advancements and procedures related to my field, this event was a great privilege because it allowed me to meet colleagues from different countries, exchange experiences, and learn from their perspectives.

While the meeting provided plenty in and out of the field, it was also a particular honor of mine to attend it actively. Namely, I gave an oral and a poster presentation highlighting my work: “Predicting First-line Immunochemotherapy Outcome in Diffuse Large B-Cell Lymphoma Patients Using ^{18}F -FDG PET/CT Parameters,”(2) which concludes that DLBCL is the most common type of non-Hodgkin lymphoma, while the majority of cancer patients achieve long-term remission with first-line immunochemotherapy treatment. However, a significant number of DLBCL patients relapse or progress. Identifying these patients early is critical for enabling an adequate adjusted risk response therapy and improve overall outcome. In our small study, we correlated several baseline potentially predictive quantitative measures on ^{18}F -FDG PET/CT, such as: total metabolic tumor volume or tMTV, total lesion glycolysis or TLG and maximal distance between the farthest lesions or Dmax. We correlated these parameters with each patient’s treatment response, as assessed by end-of-treatment ^{18}F -FDG PET/CT findings. The results showed that cancer patients that failed treatment from the start (with first-line immunochemotherapy) tended to have statistically higher values of tMTV, TLG and Dmax. The conclusion of our short presentation highlighted the increasing impact that these parameters have in outcome of lymphomas and that they may hold the key for better treatment outcomes.

For physicians and researchers (from smaller nuclear medicine communities, such as North Macedonia), the SNMMI Annual Meeting offers opportunities for exchange of experience and knowledge, where the shared ideas can be put into local practices. The future of nuclear medicine will rely on combining innovation, standardization and multidisciplinary collaboration with clinical medicine. The SNMMI Annual Meeting clearly showed that our field is moving in that direction.

Sincerely,

Dr. Slavko Tasevski

Nuclear Medicine physician and PhD student,

University Institute for Positron – Emission Tomography, Skopje

References:

1. Society of Nuclear Medicine and Molecular Imaging (SNMMI). SNMMI 2026 annual meeting highlights transformative advances in clinical practice and research [Internet]. Reston (VA): Society of Nuclear Medicine and Molecular Imaging; 2026 [cited 2026 Jul 17]. Available from: SNMMI 2026 Annual Meeting Highlights.
2. Tasevski S, Manevska N, Todorova - Stefanovski D et al. Predicting first-line immunochemotherapy outcome in Diffuse Large B-Cell Lymphoma patients using ^{18}F -FDG PET/CT parameters. Journal of Nuclear Medicine. 2026;67(1):261143.

GUIDELINES FOR AUTHORS

The Macedonian Journal of Anaesthesia (MJA) is a scientific journal of the Macedonian Society of Anaesthesia (MSA) and the Macedonian Society of Critical Care Medicine (MSCCM). The aim of this specialized medical journal is to accelerate and promote scientific achievements, new developments, clinical experiences, reviews, and discussions of controversial topics in anaesthesia, resuscitation, and intensive care, as well as other related medical fields.

The journal is published four times a year (April, June, October, and December), although additional supplements may be published when necessary. MJA publishes original articles in basic and applied research, review articles, case studies, therapeutic and technological innovations, discussions, critiques, surveys, impressions from scientific meetings, information on international conferences, and reviews of new books and other publications.

Manuscripts submitted for publication must not have been published previously. Manuscripts previously published only in abstract form are eligible for publication in the journal but must be accompanied by an additional letter to the Editor specifying the details of the abstract (abstract number, proceedings publication or DOI, date, and location).

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Manuscripts should not exceed 10 pages, excluding references.

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Only standard abbreviations should be used, as nonstandard abbreviations may confuse readers.

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At first mention, each abbreviation should be preceded by its full term, followed by the abbreviation in parentheses, unless it represents a standard unit of measurement.

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The title of the manuscript must be written in **CAPITAL LETTERS**.

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The names and addresses of the institutions with which the authors are affiliated must be provided, using superscript numbers to indicate their respective affiliations.

The abstract should not exceed 250 words and must include the objectives of the study, key elements of the methodology, a concise presentation of the results, and the conclusion. Each abstract must end with keywords listed in alphabetical order.

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- **Results**
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Review articles, case reports, articles on therapeutic and technological innovations, discussions, critiques, reports from scientific meetings, information on international conferences, and reviews of new books and other publications may follow different structures and formats.

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The Introduction should provide an overview of the literature relevant to the topic under investigation. This section should cite 3–5 key references and should not exceed two pages.

Materials and Methods

The Materials and Methods section should provide a detailed description of the research procedures

and statistical analyses performed. This section should include the study period, study design, study location, randomization or stratification procedures (with a clear description of the study groups), inclusion and exclusion criteria, research methods, types of analyses, equipment and instruments used, and reference values for the parameters examined, expressed in International System of Units (SI).

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The results should be presented clearly and concisely using text, figures, tables, and charts, placed at the appropriate locations within the manuscript, with proper titles and numbering. Additionally, all charts, figures, and tables must be submitted in a separate document accompanying the manuscript.

The titles and numbers of charts and tables should appear above them, while explanations, abbreviations, and comments should be placed below. Figure numbers and captions should appear below the corresponding figures and include appropriate explanations.

Discussion

The Discussion should emphasize the key findings of the current study and compare them with relevant findings reported in the scientific literature.

Conclusion

The Conclusion should not exceed 150 words and must be based on the relevant findings and results presented in the study.

Acknowledgments and Author Contributions

The Acknowledgments and Author Contributions sections should appear after the Conclusion and before the References section.

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For references with more than three authors, list the first three authors followed by et al.

Examples:

1. Journal Articles

Nirmala BC, Kumari G. Foot drop after spinal anaesthesia: a rare complication. *Indian J Anaesth.* 2011; 55: 78–79.

Lynch EP, Lazor MA, Gellius JE, et al. The impact of postoperative pain on the development of postoperative delirium. *Anesth Analg.* 1998;86:781–785.

2. Journal Supplements:

Azman J, Frkovic V, Bilic L, et al. Korelacija i regresija. *Acta Med Croat.* 2006;60(Suppl 1):81–89.

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Dag Stat. Mackinnon A. Available from: <http://www.mhri.cdu.au/biostats>. Accessed May 5, 2006.

Webster NR. The anaesthetist as peri-operative physician. Anaesthesia. Available from: <https://doi.org/10.1046/j.1365-2044.2000.01722.x>

References to abstracts should be identified by (abstract), while references to letters should be identified by (letter).

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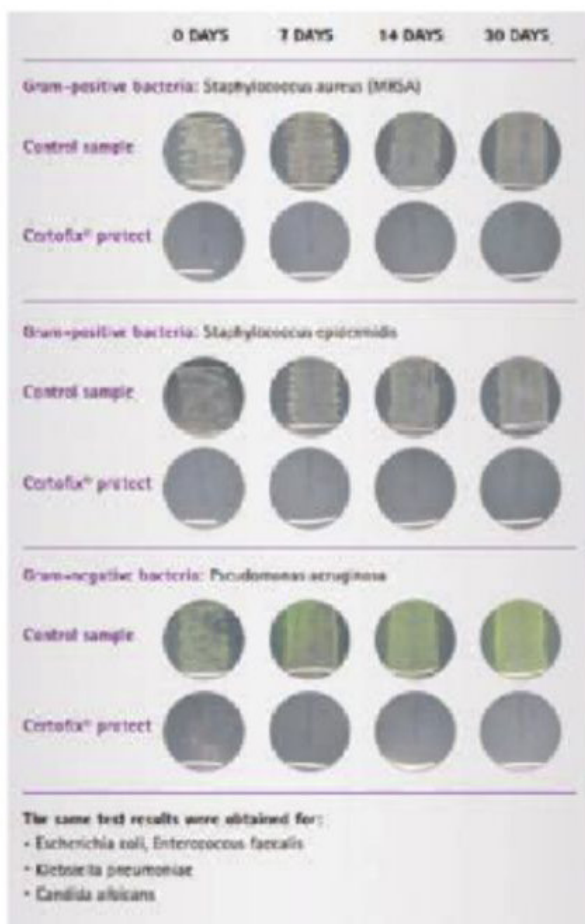
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Macedonian Journal of Anaesthesia, ISSN 2545-4404

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