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Original Article

Vasoplegia in Cardiac Surgery: A Systematic Review and Meta-analysis of Current Definitions and Their Influence on Clinical Outcomes

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Objectives: To identify differences in the reported vasoplegia incidence, intensive care unit (ICU) length of stay (LOS), and 30-day mortality rates as influenced by different vasoplegia definitions used in cardiac surgery studies.

Design: A systematic review was performed covering the period 1977 to 2023 using PubMed/MEDLINE, Embase, Web of Science, Cochrane Library, and Emcare and a meta-analysis (PROSPERO: CRD42021258328) was performed.

Setting and Participants: One hundred studies defining vasoplegia in cardiac surgery patients were systematically reviewed. Sixty studies with 20 or more patients, irrespective of design, reporting vasoplegia incidence, ICU LOS, or 30-day mortality were included for meta-analysis.

Interventions: Cardiac surgery on cardiopulmonary bypass.

Measurements and Main Results: Studies were categorized depending on the used mean arterial pressure (MAP) thresholds. Random intercept logistic regression models were used for meta-analysis of incidence and mortality. Random effect meta-analysis was used for ICU LOS. One hundred studies were reviewed systematically. MAP and cardiac index thresholds varied considerably (<50-80 mmHg and 2.0-3.5 $L \cdot min^{-1}m^{-2}$, respectively). Vasopressor dosages also differed between definitions. The reported incidence (60 studies; mean incidence, 19.9%; 95% confidence interval [CI], 16.1-24.4) varied largely between studies (2.5%-66.3%; I^2 = 97%; p < 0.0001). Meta-regression models, including the MAP-threshold, did not explain this heterogeneity. Similarly, the effect of vasoplegia on ICU LOS, and 30-day mortality was very heterogeneous among studies (I^2 = 99% and I^2 = 73%, respectively).

M.P. and E.E.C.d.W. contributed equally to this work.

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Conclusions: The large variability in vasoplegia definitions is associated with significant heterogeneity regarding incidence and clinical outcomes, which cannot be explained by factors included in our models. Such variations in definitions leads to inconsistent patient diagnosis and renders published vasoplegia research incomparable.

Key Words: vasoplegia; thoracic surgery; incidence; consensus; meta-analysis

VASOPLEGIA is a well-known complication after cardiac surgery,[1] but the fundamental pathophysiological mechanisms remain unknown. It is characterized by profound hypotension, low systemic vascular resistance (SVR), normal or increased cardiac output (CO), and blunt or absent response to fluid and vasopressor administration.[2] Persistent hypotension leads to tissue hypoperfusion and end-organ dysfunction, thereby having a predominant effect on clinical outcomes. Consequently, vasoplegia is associated with increased morbidity and mortality.[3]

Published vasoplegia definitions vary significantly in used parameters and their thresholds, such as mean arterial pressure (MAP), SVR, CO, vasopressor use, and used timeframes, demonstrating no consensus for its definition. This factor may lead to differences in reported incidences and affect the interpretation of the clinical problem.[4,5]

Vasoplegia can occur at different stages in the perioperative pathway. Accurate timing of the diagnostic assessment is crucial as this may have implications to early or delayed interventions. Furthermore, vasoplegia may occur with different prevalence and impact in different patient groups. For instance, patients suffering from heart failure (HF) or specifically undergoing surgical therapies for HF, such as insertion of ventricular assist devices or heart transplantation are particularly prone for postoperative vasoplegia.[6,7] Similarly, several other factors have been associated with the incidence of vasoplegia. Among these, the use of cardiopulmonary bypass (CPB) plays a major role.[8,9] The exposure of blood to its foreign surfaces triggers a systemic inflammatory reaction that ultimately leads to the activation of vasodilatory pathways. Therefore, a longer CPB duration predisposes patients to postoperative inflammation and hence a greater likelihood of vasoplegia. Other factors that have been recognized to influence the postoperative incidence of vasoplegia are, for example, an increased body mass index (BMI), possibly due to its association with a low-grade systemic inflammation; anemia, which is thought to be associated with reduced scavenging of nitric oxide; a potent vasodilator; and finally preoperative angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) therapy, which interfere with the renin–angiotensin–aldosterone system, one of the main regulators of the vascular tone.[10-12]

In this review, we aim to summarize published vasoplegia definitions and evaluate how these influence the reported incidence. Moreover, we will investigate the impact of vasoplegia on clinical impact such as intensive care unit (ICU) length of stay (LOS) and 30-day mortality. Finally, we will investigate the influence of MAP, year of publication, and the role of HF on the incidence and clinical impact of vasoplegia.

Materials and Methods

This review was performed according to the PRISMA statements.[13] The study protocol was registered in the International Prospective Register of Systemic Reviews (PROSPERO: CRD42021258328).

Data Sources and Searches

Five databases were searched (PubMed/MEDLINE, Embase, Web of Science, Cochrane Library, and Emcare). The MeSH terms "vasoplegia," "thoracic surgery," and "thoracic surgical procedures" were combined with keyword variations and free text (Search strategy, Supplemental material). Moreover, "cardiac surgery" and other relevant key words were used as free text to further specify and extend our search strategy. The non-English literature was excluded. The first and final searches were performed on October 18, 2021, and August 1, 2023, respectively.

Study Selection and Definitions Used

Studies defining vasoplegia in adult patients undergoing cardiac surgery were included for systematic review. Studies with 20 or more patients, irrespective of design, reporting vasoplegia incidence, ICU LOS, or 30-day mortality were included for meta-analysis. For the meta-analysis of ICU LOS or 30-day mortality, only vasoplegic patients following a per-hospital routine care protocol were considered to ensure comparability of findings. Two independent reviewers (O.P., M.v.d.S.) assessed all studies. Inclusion was decided upon full-text assessment. If necessary, a third reviewer (E.d.W.) was involved.

All variables used to define vasoplegia were chosen to capture the broad range of clinical practices in the literature and were categorized into criteria: vasodilation; hemodynamics; vasopressors; other factors such as HCO_3^- and heart rate; and timeframe (onset, duration, recovery). These criteria were used to qualitatively study and present the currently used definitions.

After data collection, MAP was chosen as the primary categorization factor because it is commonly used as a clinical indicator of low BP and is readily quantifiable (Supplementary

Figure 1). Based on the MAP thresholds that were collected from included studies 7 categories were created: (1) MAP of less than 50 mmHg, (2) MAP of less than 55 mmHg, (3) MAP of less than 60 mmHg, (4) MAP of less than 65 mmHg, (5) MAP of less than 70 mmHg, (6) MAP of less than 80 mmHg, and (7) uncategorized, if no MAP was used. If a MAP threshold was reported as treatment target per institutional protocol, rather than as vasoplegia definition criterion, this threshold was used to facilitate study categorization. A MAP of less than 55 mmHg was incorporated into the category of less than 60 mmHg, considering that only 1 study belonged in the first.[14] Such categorization was decided to allow for structured comparisons across studies to explore the variability in thresholds defining vasoplegia, its reported incidence and impact on clinical outcomes.

Although CO is crucial in vasoplegia diagnosis, it was excluded from study categorization due to the wide variability in how CO is measured and reported across studies. Nevertheless, a separate analysis of studies with a cardiac index of 2.5 $L \cdot min^{-1}m^{-2}$ or greater was performed to evaluate the reported incidence among a more homogeneous group of definitions.

All data were recorded in audit-trailed Google Spreadsheet forms. All studies were assessed for risk of bias (ROB) using the "Risk Of Bias In Non-randomized Studies of Exposure (ROBINS-E)" tool.[15]

Outcome Measures

The outcomes of this study are the vasoplegia incidence, the ICU LOS, and 30-day mortality in vasoplegic patients.

Data Synthesis and Analysis

The functions metaprop and metamean of the meta package in R (Version 3, 2022.02.1, The R Foundation for Statistical Computing, Vienna, Austria) were used for the meta-analyses. A meta-analysis on vasoplegia incidence was performed using random intercept logistic regression, overall and by category-defined vasoplegia definitions. To explore heterogeneity sources in vasoplegia incidence, meta-regression models were applied with percent of patients with HF, publication year, MAP thresholds, age, BMI, ACEi/ARB therapy, preoperative hemoglobin, and CPB duration as covariates, both univariate and multivariable. Means and standard deviations were approximated when not directly reported. Two subgroup meta-analyses (100% patients with HF and cardiac index of $\geq$2.5 $L \cdot min^{-1}m^{-2}$) were performed to evaluate incidence in more homogeneous populations. Random intercept logistic regression meta-analysis were used to pool 30-day mortality rates for vasoplegic patients. The ICU LOS was pooled using a random effect meta-analysis on a logarithmic scale because of skewness. In studies where medians, interquartile ranges, or minimum and maximum were reported, logarithmic means and standard deviations were approximated.[16] Univariable meta-regression models were used to assess the influence of percent of patients with HF, publication year, and MAP thresholds on ICU LOS and 30-day mortality; multivariable analyses were not possible because of the small study number. The I^2 statistic assessed heterogeneity with a p value of less than 0.05 considered statistically significant.

Results

Study Characteristics and Bias

The search strategy resulted in inclusion of 100 studies for review (Figure 1). Included studies were published between 1977 and 2022. For the meta-analysis of vasoplegia incidence, ICU LOS, and 30-day mortality, 60, 21 and 16 studies were included respectively.

In the ROB assessment, all included studies were found to have "some concerns," primarily due to issues related to patient selection, unknown postexposure interventions and the nonexclusion of other etiologies of hypotension (Supplementary Table 1 [A,B,C]).[17] Specifically, studies involving HF and endocarditis populations exhibited high ROB, which potentially influenced the reported ICU LOS and 30-day mortality.

Overview of Vasoplegia Definitions

Published definitions are summarized in Supplementary Table 2. The overall parameters used and variations in thresholds found are summarized in Table 1. The lack of a universally accepted definition was explicitly mentioned in 34 studies.[4,5,7,18-48] Most investigators have not provided explanations for their chosen definition[3,18,26,28,34,48-92] whereas others used a previously published definition.[6,11,12,20,21,23-25,27,29-33,35-45,47,93-108] Two studies identified the arbitrary nature of their definition.[14,51] Others used a pooled[7,40,44] or a self-developed definition.[4,5,19,22] A survey among German heart centers was used in another study to derive their vasopressor threshold.[46] In addition, severity categories of vasoplegia were defined by some authors.[18,20,23,38,40,98] Most of the studies (83 studies) utilized MAP for the definition of vasoplegia as an indication for the hemodynamic condition of the patient. The rest of the studies (17 studies) used other parameters, such as systolic blood pressure (SBP), SVR, or vasopressor dosage.

Vasodilation Criterion

Various thresholds of MAP, SBP and SVR were used as indicators of vasodilation (Supplementary Table 2). Twenty studies did not use any MAP threshold for the diagnosis and treatment of vasoplegia.[28,31,44,47,51,52,54,55,57,59,64,67,73,75,79,81,84,97] Forty-one studies used an SVR threshold in their definition and 14 studies used its index[6,23,25,29,36,37,45,51,63,65,69,

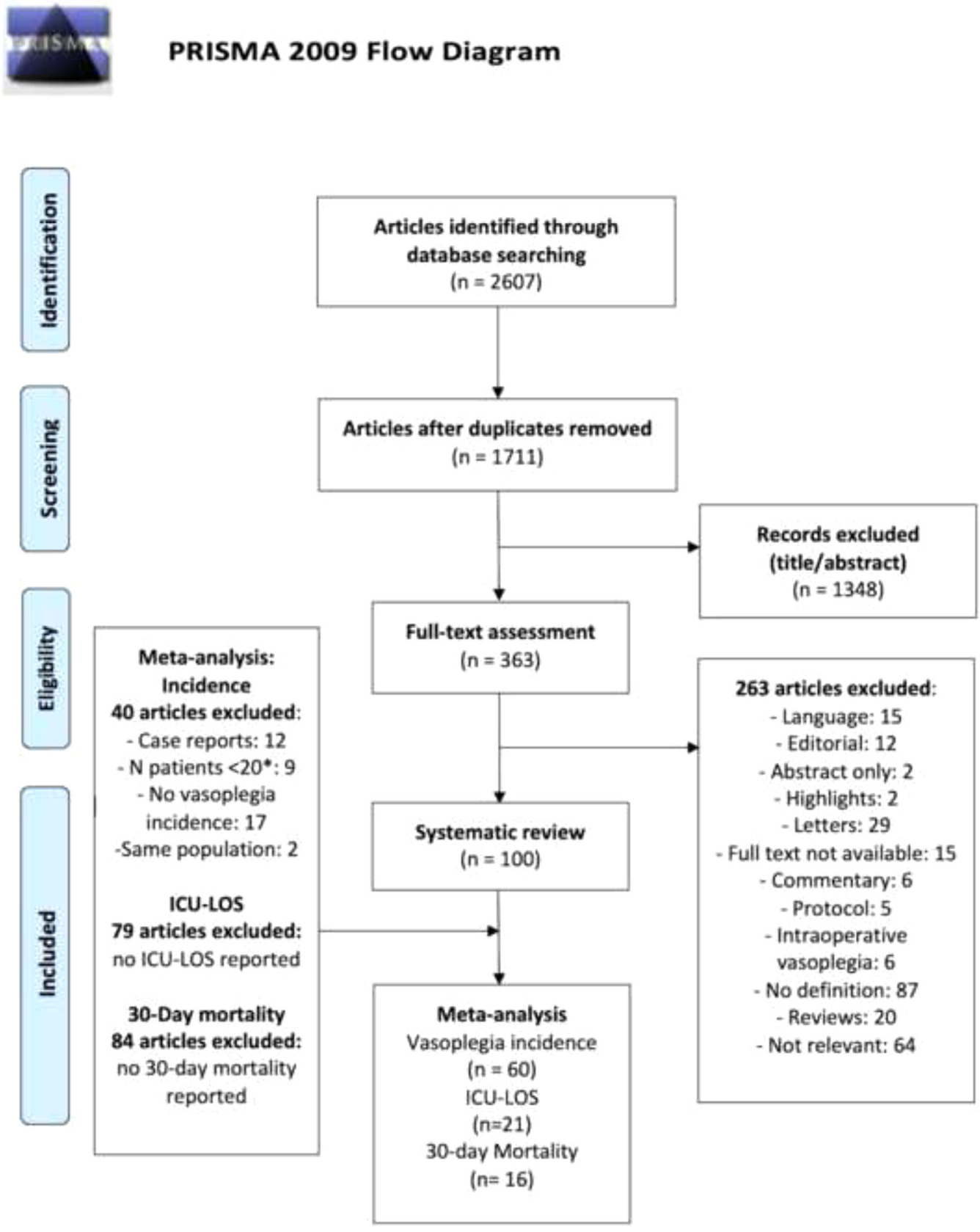

Figure 1. A detailed PRISMA flowchart. *Studies with fewer than 20 patients that would contribute little information were exclude.

Table 1
Parameters and Thresholds Used in Published Definitions

Vasodilation Criterion	Hemodynamic Criterion	Vasoactive Drugs	Timeframe	Other Criteria
MAP ≤50-80 mmHg	CI ≥2.0-3.5 L·min^{-1}m^{-2}	Type: Norepinephrine Vasopressin Epinephrine Dobutamine Phenylephrine Methylene blue Epinephrine Vitamin B_{12} Metaraminol	Onset: <30 minutes to 4 days after CPB	HR > 80/min
SVR ≤500-900 dynes·seconds·cm^{-5}	CO >4-5 L·min^{-1}	Dosage or NEE variations	Duration: single reading up to > 24 hours	Mixed/central venous oxygen saturation >60%-70%
SVR index ≤600-1800 dynes·seconds·cm^{-5}m^{-2}	LVEF >50%-55%	Combination of one or more agents		Oxygen extraction <35%
SBP <70-90 mmHg	CVP <5 or >8 mmHg			Bicarbonate levels < 19-20 mEq/L
	PCWP <10 mmHg			

CI, cardiac index; CVP, central venous pressure; HR, heart rate; LVEF, left ventricular ejection fraction; NEE, norepinephrine dosage equivalent; PCWP, pulmonary capillary wedge pressure.

[78,89,109]; one used both.[85] The SVR threshold varied between less than 500 and 900 dynes·seconds·cm^{-5}, with the most common being less than 800 dynes·seconds·cm^{-5}. The reported thresholds of SVR index varied between 600 and 1800 dynes·seconds·cm^{-5}m^{-2}. Six studies used the SBP to define vasoplegia with the threshold varying between 70 and 90 mmHg.[55,57,59,62,76,96]

Hemodynamic Criterion (CO/Index, Left Ventricular Ejection Fraction, Filling Pressures, and Cardiac Contractility)

From the hemodynamic variables, cardiac index was the most reported one. However, two studies reported the CO,[56,57] whereas one reported both CO and index.[96] A cardiac index of greater than 2.5 L·min^{-1}m^{-2} was the most popular threshold. Overall, large heterogeneity was seen among studies and cardiac index thresholds varied between greater than 2.0 and 3.5 L·min^{-1}m^{-2}. However, the variability was minor regarding the left ventricular ejection fraction (>50%-55%).[18,33,41,69,98,103] Filling pressures were used as diagnostic criterion in 29 studies. Central venous pressure of less than 5 mmHg and pulmonary capillary wedge pressure of less than 10 mmHg were frequently used as cut-offs.[3,60,64,74,79,85,106] In contrast, other investigators defined vasoplegia when the central venous pressure was greater than 8 mmHg.[6,18,19,45,66,76,93,105]

For the description of patients' hemodynamic condition, differences were found in the given variables and monitoring methods used to acquire these. Invasive measurements were performed in the majority of studies using a pulmonary artery catheter,[3-7,11,12,14,18,23-26,28,29,32,41,43-47,51,55,56,58,60,61,63-74,76,78,85-87,89,93-97,100,102,107] pulse contour analysis,[5,27,29,69,94,99,101] or the minimally invasive FloTrac system.[37,48] Twenty-five studies did not provide any information on how CO/index was measured.[20-22,33,35,36,40-42,49,50,53,77,80,81,83,84,88,90,91,103-106,108] Echocardiography aided the diagnosis of vasoplegia by confirming normal cardiac contractility in 23 studies.[7,18,21,27,30,31,33,37,39,41,59,61,68-72,79,88,98,101,103,108] Last, assessment of filling pressures was used in 29 studies.[3,6,18,19,30,36,37,45,60-64,66,68-70,72,74,76,77,79,83,85,90,93,94,105,106]

Vasopressor Use

Vasopressor support was described in 77 articles; however, not all investigators specified the doses required to diagnose vasoplegia. Among studies that did apply a dosage threshold, norepinephrine greater than 0.1[5,22,46,62,65,69,76,89,109] or greater than 0.2 μg·min^{-1}kg^{-1}[4,11,12,34,36,102,104] was used most often. Combined use of vasopressor and/or inotropic agents was considered necessary to assess vasoplegia in a few studies.[21,22,24,44,78,84] Vasopressor support was in some definitions the only criterion for the diagnosis of vasoplegia.[31,67,84,92,97]

Timeframe and Other Criteria

Lack of agreement was also seen in the reported timing of vasoplegia incidence (<30 minutes to 4 days after CPB) and the required duration (single reading up to >24 hours).

Other reported criteria included heart rate of greater than 80 beats/min,[69] mixed/central venous oxygen saturation of greater than 60%[26,69,108] or 70%[18,105] and oxygen extraction of less than 35%,[70] and 5 studies described bicarbonate levels of less than 19 mEq/L[59] or greater than 20 mEq/L[47,52,54,73] in the diagnosis of vasoplegia. The exclusion of other causes of postoperative hypotension such as cardiogenic, hypovolemic, or septic shock was highlighted by some investigators.[4,6,7,21,24,26-30,33,36,37,39,41,45,46,49,53,59,60,65,66,69,71,85,87-89,91,96,98,99,103,108]

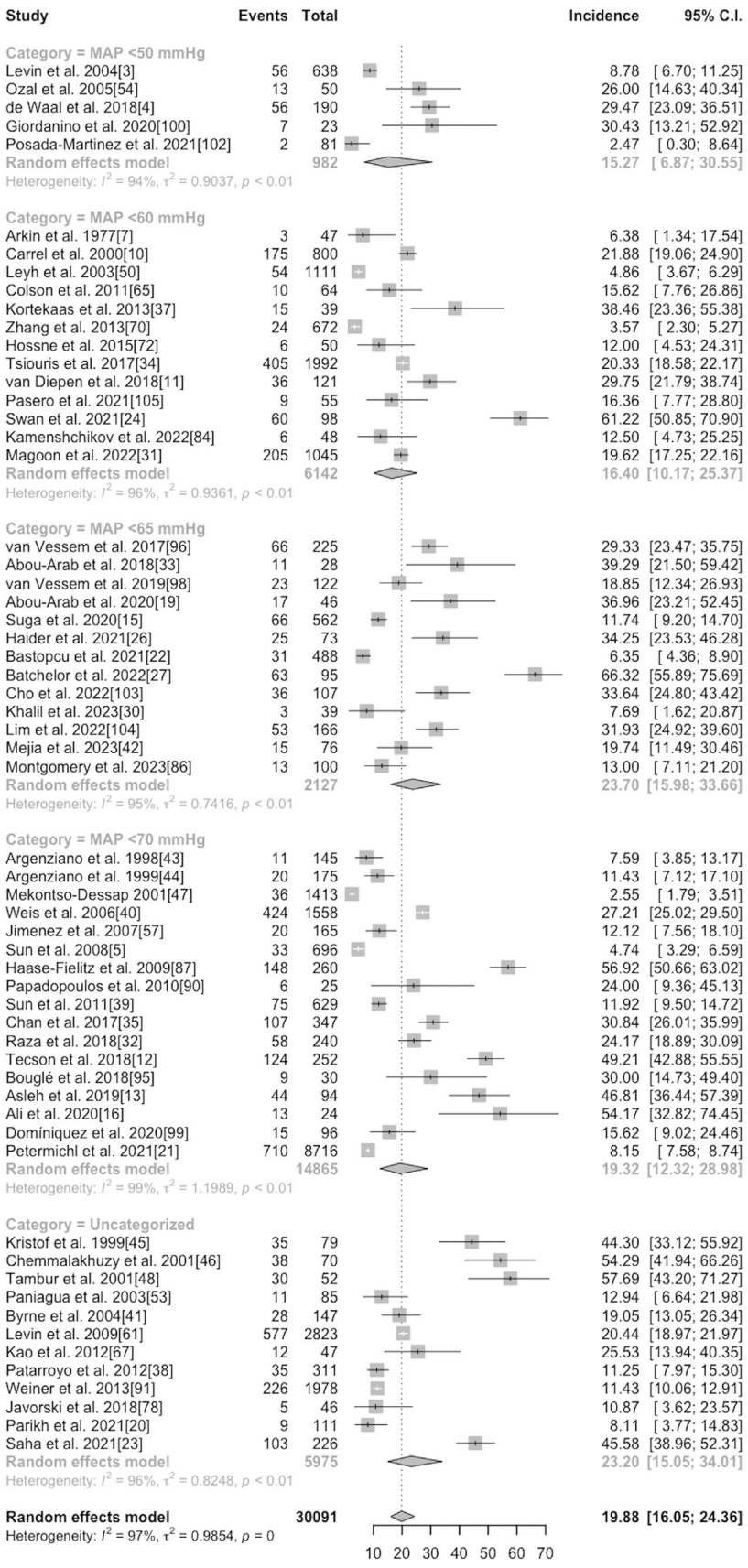

Figure 2. Incidence of vasoplegia according to categorized vasoplegia definitions: a Forest plot with the results of a random-effects model. CI, confidence interval.

Vasoplegia Incidence

Reported vasoplegia incidences differed largely between studies and varied between 2.5% and 66.3% (Figure 2). The random-effects meta-analysis yielded a mean incidence of 19.9%, (95% confidence interval [CI], 16.1%-24.4%) with large heterogeneity (I^2 = 97%; p < 0.0001) (Figure 2, Supplementary Table 3). Heterogeneity was also large within the predefined MAP categories. The additional analysis performed in studies with cardiac index of 2.5 L·min^{-1}m^{-2} or greater did not show any significant difference regarding heterogeneity (mean incidence, 14.7%; 95% CI, 9.8%-21.7; I^2 = 98%; p < 0.0001) (Supplementary Figure 1).

In the univariable meta-regression analysis, MAP cut-offs did not influence vasoplegia incidence significantly (p = 0.7). More specifically, when a MAP of less than 60 mmHg was used as a cut-off, patients had a 1.1 higher odds of being classified as vasoplegic, than when a MAP of less than 50 mmHg was used. The highest odds ratio was observed for a MAP of less than < 65 mmHg and uncategorized (odds ratio, 1.7). Patients with a MAP of less than 70 mmHg had a 1.3 higher odds than patients with a MAP of less than 50 mmHg. These differences did not reach statistical significance, and no specific pattern between vasoplegia incidence and MAP cut-offs could be distinguished. Similarly, neither the year of publication nor other parameters such as age, BMI, hemoglobin, ACEi/ARB therapy, and CPB duration influenced vasoplegia incidence (Table 2). There was a significant association between percent of patients with HF and vasoplegia incidence (54 studies) with an odds ratio of vasoplegia of 1.01 per percentage increase in percent of patients with HF (Table 2, Figure 3). This result yielded an estimated vasoplegia incidence of 14% in studies without patients with HF and 31% for studies with 100% patients with HF. The effects in the multivariable meta-regression model were similar.

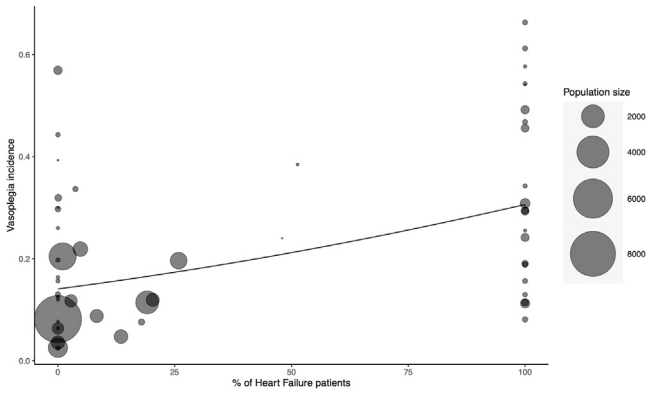

Figure 3. Bubble plot with a fitted metaregression line of the relationship between vasoplegia incidence and percent of patients with HF.

In the subgroup of studies with 100% HF, large heterogeneity in vasoplegia was also observed (I^2 = 94%; tau^2 = 0.7; p < 0.0001) (Supplementary Table 4, Supplementary Figure 2), and this finding was true also within the different MAP categories. Meta-regression analyses with MAP category or year of publication as an independent variable did not explain the between-study heterogeneity (I^2 = 94% and 95%, respectively) (Supplementary Table 5).

Table 2
Estimates of Odds Ratios (Effects) of Different Factors in Models of Single Covariates (Univariable Regression) and in Combination (Multivariable Regression) for the Effect on Vasoplegia Incidence

Variables	No. of Studies	Odds Ratio	95% CI	*P* Value	Tau^2	I^2
Univariable						
Percentage of patients with HF	54	1.01	1.01-1.02	0.0003	0.81	97%
Year of publication	60	1.03	0.996-1.06	0.09	0.94	98%
MAP category	60				0.95	98%
<50		*Reference				
<60		1.1	0.4-3.2	0.9		
<65		1.7	0.6-4.99	0.3		
<70		1.3	0.5-3.7	0.6		
Uncategorized		1.7	0.6-4.9	0.4		
Age	52	0.99	0.95-1.03	0.6	0.92	98%
BMI	36	0.94	0.86-1.02	0.1	0.80	96%
Hemoglobin	14	0.89	0.66-1.20	0.4	0.50	94%
Percentage of patients on ACEi/ARB	37	1.0	0.99-1.0	0.5	0.83	97%
CPB duration	47	1.0	0.99-1.0	0.9	0.87	97%
Multivariable						
Percentage of patients with HF	54	1.01	1.004-1.02	0.0006	0.76	96%
Year of publication		1.02	0.98-1.05	0.3		
*Category						
MAP <60		1.5	0.6-4.2	0.4		
MAP <65		1.6	0.6-4.3	0.4		
MAP <70		1.2	0.5-3.1	0.7		
Uncategorized		1.4	0.5-3.9	0.5		

* Reference: MAP <50 mmHg.
CI, confidence interval.

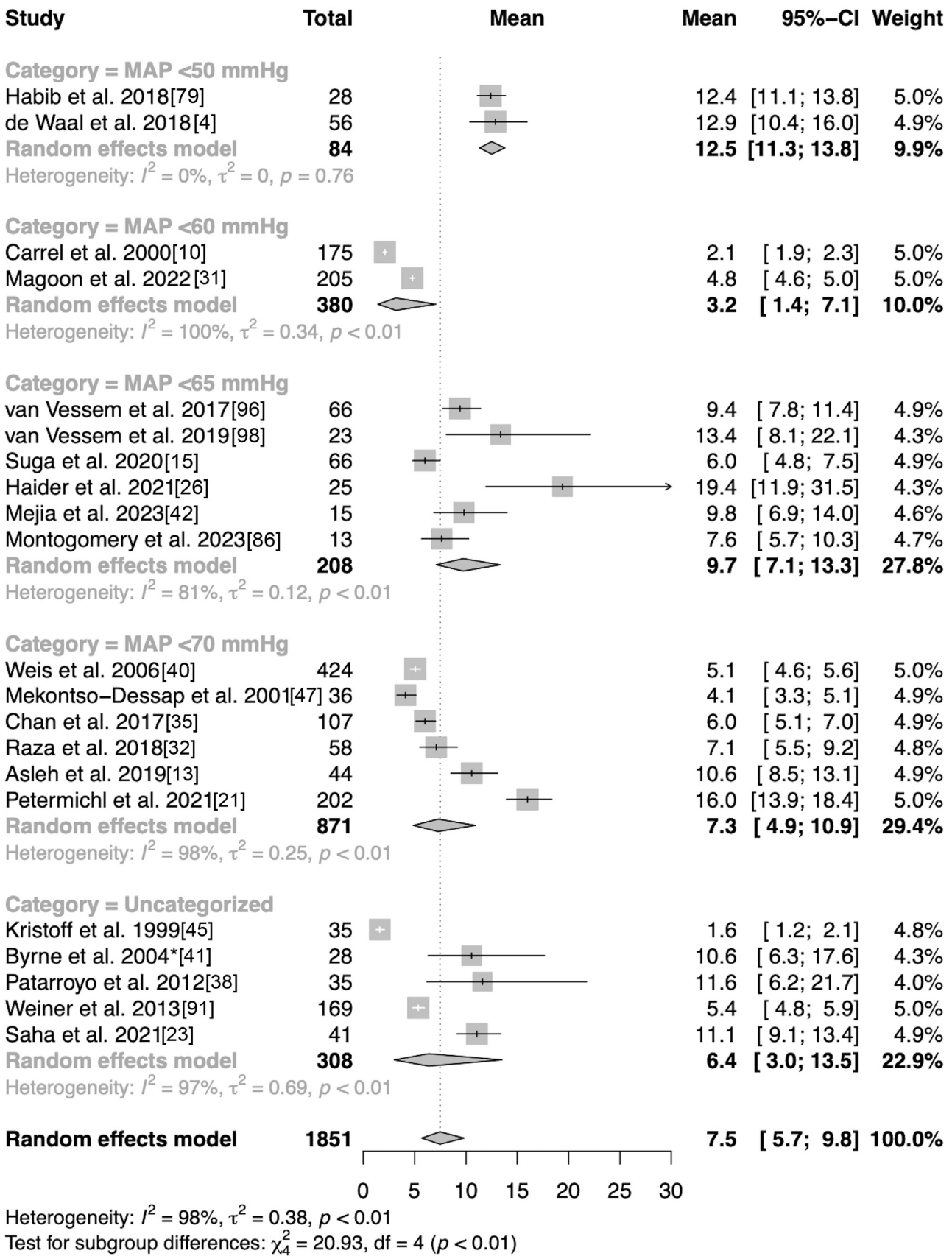

Figure 4. Length of ICU stay in days according to categorized vasoplegia definitions: a Forest plot with the results of a random-effects model. CI, confidence interval; SD, standard deviation. *Byrne et al. 2004: the given range was assumed to be minimum and maximum

ICU LOS

The mean ICU LOS in vasoplegia patients was 7.5 days based on the data from 19 studies (95% CI, 5.7-9.8 days). Reported mean ICU LOS between studies varied between 1.6 and 19.4 days (I^2 = 99%; p < 0.01) (Figure 4). Large heterogeneity was also found for studies within the same MAP category. In the meta-regression analysis, a unit increase in percent of patients with HF results in a 1.006 times higher ICU LOS (95% CI, 1.000-1.011). The mean LOS also became 1.057 times larger per year increase in publication year (95% CI, 1.03-1.08; p < 0.0001) (Supplementary Table 6). The different MAP categories did not significantly influence the LOS (p = 0.078).

Thirty-Day Mortality

Sixteen studies provided data on mortality. Reported mortality rates for vasoplegia varied between 2.3 and 36%. A random-effects meta-analysis showed a mean incidence of 13.7% (95% CI, 9.2%-19.8%), with large heterogeneity (I^2 = 73%; tau^2 = 0.5; p < 0.01) (Supplementary Figure 3). Neither of the 3 univariable regression models could explain the source of this heterogeneity (Supplementary Table 7).

Discussion

We have observed large discrepancy between used vasoplegia definitions, specifically on the hemodynamic parameters such as MAP, cardiac index, and the requirement for vasopressor use and dosage, their cut-off values, and timing and duration of vasoplegia. In addition, large heterogeneity was found in the reported vasoplegia incidence, ICU LOS, and mortality rates. The percentage of included patients with HF could only partly explain the increased vasoplegia incidence in studies with patients with HF. Therefore, the lack of a unified vasoplegia definition and the substantial differences in the parameters used may have resulted in different patients being identified as suffering from vasoplegia. This finding implies that results from many years of research might be incomparable between centers that use different definitions. Thus, our meta-analysis highlights this clinical problem and calls for a new international consensus to better define vasoplegia.

The discrepancies in published definitions are substantial. Our results regarding these discrepancies between different center are also representative of more recently published studies.[110,111] MAP and SVR are used commonly as indicators of vasomotor tone, although their thresholds vary significantly. For this meta-analysis, we categorized definitions in predefined groups based on MAP to detect possible within-group correlations, yet significant heterogeneity persisted. Careful investigation revealed variability in other parameters, such as cardiac index, vasopressor dosages, and timeframe. Similar results were found when analyzing studies with comparable cardiac index thresholds. Important differences were also observed in the monitoring method (such as PAC and echocardiography) chosen to obtain certain hemodynamic variables which questions the comparability of the collected variables. The chosen technique may influence the precision and reliability of hemodynamic measurements considering that PAC provides direct CO measurements, whereas echocardiography relies on operator-based estimations.[112] The lack of consensus is obvious, and, so far, no substantial arguments have been provided to consider the superiority or inferiority of a specific definition. Although there have been some individual efforts to construct a new or unifying definition, collective efforts are needed to reach this goal to facilitate further research into this important issue for cardiac surgery patients.

Even though HF surgery has been associated with an increased risk of postoperative vasoplegia, which could have skewed the results of this study, our meta-regression model could not explain the large heterogeneity in reported incidence by the presence or absence of HF. Furthermore, the subgroup analysis revealed substantial heterogeneity in vasoplegia incidence among studies in patients with HF. Considering the substantial variations in the chosen variables and thresholds in published definitions, these differences might have affected vasoplegia incidence even in a more homogeneous selection of studies. Nevertheless, the mean incidence from HF studies was higher compared to studies with mixed populations. Therefore, the percentage of included patients with HF could only partially justify this large heterogeneity in the estimated incidence. This result was expected considering that preexisting HF is an independent predictor of vasoplegia.[6]

The current meta-analysis demonstrated significant heterogeneity in ICU LOS and 30-mortality rates for vasoplegia patients, likely due to variations in vasoplegia definitions. Moreover, differences in baseline characteristics, risk profiles, and ICU discharge protocols might also explain the large heterogeneity observed. Interestingly, publication year seems to affect the mean ICU LOS significantly. However, after careful examination of our data, this effect is caused mainly by the two oldest studies by Kristof et al.[51] and Carrel et al.,[18] which reported very low mean LOS (1.6 and 2.1 days). In both studies, consecutive patients undergoing coronary bypass or valve surgery were included, meaning that more complex operations such as HF surgery were excluded. Also, nowadays we have vast surgical and technological possibilities to better monitor and treat higher-risk patients and to perform more challenging procedures. These reasons, in combination with the increasing awareness of postoperative vasoplegia, may explain the effect of publication year on ICU LOS. Another interesting observation is that the MAP threshold used to define vasoplegia did not seem to influence the reported ICU LOS and 30-day mortality rates. More specifically, lower MAP-thresholds, which would possibly lead to the diagnosis of “sicker” patients, did not translate into a linear increase in ICU LOS and mortality. Although it is difficult to draw safe conclusions, considering that other diagnostic parameters also differed, this might indicate that lower blood pressure thresholds might not necessarily be associated with worse clinical outcomes in some patients and that more personalized blood pressure targets should be aimed for during therapeutic strategies.[113,114] Nevertheless, this observation should be approached with caution, especially

considering the results of the study by Wesselink et al.,[115] which suggest that organ injury might occur when MAP decreases below 80 mmHg for more than 10 minutes.

Published vasoplegia definitions vary significantly. Due to these inconsistencies in definitions, patients with different clinical characteristics might have been diagnosed as vasoplegic under different definitions. Thus, published research findings of the last decades might be rendered incomparable between different centers and studies. Therefore, it is difficult to explore a relation between underlying mechanisms, such as patient characteristics, inflammatory events, and procedural factors with the incidence and severity of vasoplegia and its effects on clinical outcomes. Thus, a unified definition must be established based on evidence and multidisciplinary expert opinions including the ultimate criteria for diagnosing vasoplegia and their cut-off values. A generally accepted vasoplegia definition will enable comparison of research results supporting a better understanding of its mechanisms, prediction, prevention, and treatment.

Limitations

This meta-analysis offers valuable insights, but limitations necessitate cautious interpretation. Included studies' quality directly impacts our findings, and the ROB assessment identified potential concerns. Studies using broader vasoplegia definitions ("some concerns") might introduce measurement bias for ICU LOS and 30-day mortality. Additionally, unknown postexposure interventions ("some concerns") introduce uncertainty about confounding factors. Another important factor that may hinder the comparability of different studies is possible variations in the formulations of commonly used vasopressors which might make reported dosages incomparable.[116] Studies in specific patient populations, such as patients with HF, potentially influenced ICU LOS and 30-day mortality, highlighting the difficulties in isolating the effect of vasoplegia on clinical outcomes. Despite these concerns, all studies were included to ensure a comprehensive analysis across a representative range of clinical scenarios. Sensitivity analysis only in HF studies confirmed that the variability in definitions influences the reported incidence also in a more homogeneous population. Furthermore, categorizing studies based on treatment target ("speculative") might have introduced inaccuracies. However, given the significant heterogeneity in definitions and meta-analysis results, alternative categorization methods are unlikely to alter the conclusions. The inclusion of older studies in light of evolving practices, variable monitoring methods, and excluding the non-English literature necessitates further caution.

Conclusions

Our study addresses the variability in vasoplegia definitions and reported incidence across studies. Large heterogeneity between reported vasoplegia incidence was observed. Only the proportion of included patients with HF was associated with an increase in the estimated incidence. However, this could not justify the substantial heterogeneity found. The inherent variations in vasoplegia definitions may have led to inconsistencies in patient diagnosis which could therefore signify that the so far published results from vasoplegia research are incomparable. This variability reflects the real-world challenge of standardizing vasoplegia diagnosis and treatment protocols. A unified definition is necessary to generate comparable research findings. A consensus Delphi study among international experts could help establish criteria for defining vasoplegia with worldwide implementation.

Registration

The systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 31 May 2021 and was last updated on 24 October 2023 (registration number: CRD42021258328).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Olga Papazisi: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Marnix M. van der Schoot:** Writing – review & editing, Writing – original draft, Software, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Remco R. Berendsen:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Sesmu M. Arbous:** Writing – review & editing. **Saskia le Cessie:** Writing – review & editing, Methodology, Formal analysis. **Olaf M. Dekkers:** Writing – review & editing, Methodology, Formal analysis. **Robert J.M. Klautz:** Writing – review & editing. **Nandor Marczin:** Writing – review & editing. **Meindert Palmen:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Eric E.C. de Waal:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2025.02.027.

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