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Incidence of multiple organ failure in adult polytrauma patients: A systematic review and meta-analysis

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BACKGROUND:	Postinjury multiple organ failure (MOF) is the leading cause of late death in trauma patients. Although MOF was first described 50 years ago, its definition, epidemiology, and change in incidence over time are poorly understood. We aimed to describe the incidence of MOF in the context of different MOF definitions, study inclusion criteria, and its change over time.
METHODS:	Cochrane Library, EMBASE, MEDLINE, PubMed, and Web of Science databases were searched for articles published between 1977 and 2022 in English and German. Random-effects meta-analysis was performed when applicable.
RESULTS:	The search returned 11,440 results, of which 842 full-text articles were screened. Multiple organ failure incidence was reported in 284 studies that used 11 unique inclusion criteria and 40 MOF definitions. One hundred six studies published from 1992 to 2022 were included. Weighted MOF incidence by publication year fluctuated from 11% to 56% without significant decrease over time. Multiple organ failure was defined using four scoring systems (Denver, Goris, Marshall, Sequential Organ Failure Assessment [SOFA]) and 10 different cutoff values. Overall, 351,942 trauma patients were included, of whom 82,971 (24%) developed MOF. The weighted incidences of MOF from meta-analysis of 30 eligible studies were as follows: 14.7% (95% confidence interval [CI], 12.1–17.2%) in Denver score >3, 12.7% (95% CI, 9.3–16.1%) in Denver score >3 with blunt injuries only, 28.6% (95% CI, 12–45.1%) in Denver score >8, 25.6% (95% CI, 10.4–40.7%) in Goris score >4, 29.9% (95% CI, 14.9–45%) in Marshall score >5, 20.3% (95% CI, 9.4–31.2%) in Marshall score >5 with blunt injuries only, 38.6% (95% CI, 33–44.3%) in SOFA score >3, 55.1% (95% CI, 49.7–60.5%) in SOFA score >3 with blunt injuries only, and 34.8% (95% CI, 28.7–40.8%) in SOFA score >5.
CONCLUSION:	The incidence of postinjury MOF varies largely because of lack of a consensus definition and study population. Until an international consensus is reached, further research will be hindered. (<i>J Trauma Acute Care Surg.</i> 2023;94: 725–734. Copyright © 2023 The Author(s). Published by Wolters Kluwer Health, Inc.)
LEVEL OF EVIDENCE:	Systematic Review and Meta-analysis; Level III.
KEY WORDS:	Multiple organ failure; multiple injuries; trauma; shock; systemic inflammatory response syndrome.

Postinjury multiple organ failure (MOF) is a syndrome that was first described in the late 1970s, the period where critical care medicine advanced to the level where an isolated organ failure did not lead to death.^{1,2} However, as patient survival from the acute impact of trauma has increased, treating complications like MOF, which accounts for 51% to 61% of late deaths in trauma patients, has become increasingly important.^{3,4}

Although MOF has reportedly become less lethal over the decades, it remains a prevalent and costly syndrome to treat.^{3–5} Management of MOF patients is intensive and disproportionately consumes health care resources. Multiple organ failure cohorts in trauma have mean intensive care unit length of stays of more than double those without MOF with same injury severity, and mortality

rates have been reported in excess of 50% as opposed to 10% to 15% in those without.^{6,7} Even among survivors of MOF, the long-term consequences are far-reaching at a health care system and individual level, adding significant morbidity to patients' lives.⁸

Despite almost universal agreement that MOF is a leading cause of late death in trauma cohorts, there is no universally accepted definition of what constitutes MOF as an entity, from both a clinical and pathophysiological perspective. Knowledge derived from sepsis and other physiological insults has been overlaid in the trauma context and seemingly accepted without any convincing evidence. Multiple scoring systems have been developed for both research and clinical applications, which evaluate a patient's cardiovascular, hepatic, renal, neurological, coagulation, and respiratory function.^{9–12} However, there is no universally accepted scoring system for MOF in trauma, nor an accepted cutoff value for these scores. Most importantly, there is a lack of widespread validation for these scores in the trauma context. The lack of an accepted definition gives rise to the significant variation in incidence of MOF between various institutions, as the incidence of MOF is the quotient of the definition (numerator) and the overall study population (denominator), both of which are arbitrary.

As a global trauma society, it seems critically urgent that a universally accepted definition of MOF is defined to allow for further research on this topic. The goal of this review was to systematically describe the incidence of MOF using various definitions of MOF and in different patient populations. The secondary aim was to describe the change in incidence over time.

PATIENTS AND METHODS

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines¹³ (Supplemental Digital Content, Supplementary Data 1, <http://links.lww.com/TA/C881>). The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42018095284).

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Search Strategy

A systematic search was performed on December 9, 2022, using the Cochrane Library, EMBASE, MEDLINE, PubMed, and Web of Science databases. Search terms were the following: (“Trauma” OR “Injury*” OR “Post injury” OR “Post-injury”) AND (“Multiple organ failure” OR “Organ failure” OR “MOF” OR “Organ dysfunction” OR “Multiple organ dysfunction syndrome” OR “MOD” or “MODS”) AND (“Epidemiology*” OR “Incidence*” OR “Predict*” OR “Prediction model” OR “Outcome” OR “Sequelae” OR “Risk factor” OR “Mortality” OR “Prevalence”). The results were limited to articles published in the English or German languages, from 1977 onward, when MOF was first described by Eiseman et al.²

The results returned by the search were exported to the End-Note X9 software (Clarivate Analytics, London, United Kingdom), where duplicates were removed. The remaining articles were screened by their titles and abstracts for relevance to MOF. Articles were subsequently uploaded to the Covidence Systematic Review Software (Veritas Health Innovation, Melbourne, Australia; available at www.covidence.org), where full-text evaluation was performed by two independent investigators. Disagreements were resolved by discussion between both investigators and adjudication by a third investigator. Reference lists of included articles, books, and book chapters were manually screened for relevant articles.

Study Selection

Studies that reported the incidence of MOF, which was the quotient of the number of patients who met criteria for MOF (numerator) and the study population among whom the incidence of MOF was reported (denominator), were included. This search included observational and interventional studies that reported data pertaining to incidence of MOF in countries that have similar population demographics; mode of trauma; health care systems, particularly emergency medical services; and advanced trauma care models to those of Australia. Studies that focused on multiple-organ dysfunction syndrome, a term that has been used interchangeably with MOF, was included.¹⁴ Studies that concentrated on adult trauma patients were included. Studies that investigated systemic inflammatory response syndrome or acute respiratory distress syndrome without reference to MOF or multiple organ dysfunction syndrome were excluded. Studies that concentrated on pediatric populations and nonmechanical trauma, such as burns, drowning, hanging, or electrocution, were excluded. However, secondary consequences of trauma, such as sepsis or hypothermia leading to MOF, were included.

Because of the inherent challenges of researching both polytraumatized patients and MOF owing to a lack of globally accepted definition, the authors were concerned that including all studies regardless of their inclusion criteria would add significant heterogeneity, as the included studies' sample populations play a key role in the calculated incidence. The inclusion criteria and mechanism of injury were examined for all studies, and the individual papers were assessed and included if they met a generally accepted mechanism and reasonable threshold for high risk for MOF (i.e., Injury Severity Score greater than 15, base deficit on arrival to the emergency department of greater than 6, need for hemorrhagic resuscitation etc.). Studies that did not specify a MOF scoring system and cutoff value, or had cohorts that used a MOF definition that was not used by ≥ 3 other cohorts, were excluded because these factors

limited the external validity of their results. Where a study was included in our meta-analysis, the same patient was not represented twice. Studies with overlapping recruitment periods at the same institution or databases as another study were carefully examined, and only the study with the largest sample size was included.

Data Collection

Data relating to demographic information of the patients, inclusion and exclusion criterion for each respective study, and definitions of MOF, in addition to data on incidence, predictors, and outcomes of MOF, were extracted and were uploaded to the Covidence Systematic Review Software. Data extraction was independently completed by two investigators. When not provided explicitly, the number of MOF patients was computed by multiplying the reported percentages and total number of patients. Multiple cohorts were created from one study if a study had (1) different inclusion criteria for different groups and/or (2) defined MOF differently for different groups. For example, if a single study reported the incidence of MOF in two cohorts with the same inclusion criteria but used two different scoring systems, then there would be two different cohorts, with different incidences of MOF.

Data Synthesis

Pooled MOF Incidence Rate by Publication Year

OpenMeta[Analyst] (CEBM, Brown University, RI) was used to calculate the weighted incidence of MOF among included studies by publication year.

Meta-analysis of MOF Incidence by MOF Definition and Inclusion Criteria

OpenMeta[Analyst] (CEBM) was used to perform meta-analysis and to generate forest plots. Included studies were analyzed using the DerSimonian-Laird random-effects method to calculate the weighted incidence of MOF (95% confidence interval) among subgroups with different inclusion criteria and MOF definitions. A minimum of three studies were required to generate a forest plot.

Where possible, an additional analysis was performed for subgroups that had the same MOF score threshold and inclusion criteria (i.e., blunt mechanism).

Heterogeneity

Heterogeneity was quantified using the I^2 test, which is not inherently dependent upon the number of studies considered.¹⁵ I^2 values ranged from 0% (homogenous) to 100% (heterogenous). However, a random-effects model was used for all analyses.

Quality Appraisal

Included studies were appraised using a modified Oxford Center for Evidence-based Medicine rating and Mixed Methods Appraisal Tool.^{16,17}

RESULTS

Study Selection

The initial search returned 11,440 articles, of which 3,581 were duplicates, resulting in a total of 7,859 articles. Screening based on title and abstracts for relevance to MOF excluded

7,017 articles, leaving 842 articles for full-text review. A total of 558 full-text manuscripts were excluded based on their study designs, patient demographics, mechanisms of injury, or due to inadequate MOF incidence data. Of the remaining 284 full-text articles that reported the incidence of MOF, 178 manuscripts were excluded because of either not using a MOF definition used by at least 3 other studies or for reporting MOF incidence based on specific mechanism or demographic factor. Nineteen studies comprising 55 cohorts were excluded because they focused on specific mechanism or demographic factors: penetrating mechanism ($n = 3$ cohorts), age younger than 65 years ($n = 25$ cohorts), age older than 65 years ($n = 4$ cohorts), normal body mass index (BMI) ($18.5\text{--}25\text{ kg/m}^2$; $n = 4$ cohorts), overweight BMI ($25\text{--}29.9\text{ kg/m}^2$; $n = 4$ cohorts), obese BMI ($30\text{--}39.9\text{ kg/m}^2$; $n = 7$ cohorts), morbidly obese BMI ($>40\text{ kg/m}^2$; $n = 2$ cohorts), alcohol intoxication ($n = 3$ cohorts), and no alcohol intoxication ($n = 3$ cohorts). A further 159 studies were excluded because the reported MOF definitions were not used by ≥ 3 other studies. Overall, 113 cohorts from 106 studies were included in the qualitative synthesis. A supplement file shows this in more detail (Supplemental Digital Content, Supplementary Table 1, <http://links.lww.com/TA/C989>).

For meta-analysis, a further 25 studies were excluded because they had overlapping enrolment periods at the same institutions with another included study, and 52 studies were excluded because they had overlapping enrolment periods of

analysis of the same database/participating institutions. Ultimately, 30 cohorts from 29 studies were included for quantitative synthesis (Fig. 1).

Included Articles

Of the included studies, 4 of the 106 reported the incidence of MOF in multiple cohorts within the same study. These cohorts either had different inclusion criteria or MOF definitions. Sauaia et al.⁹ and Sauaia et al.¹⁸ reported the incidence of MOF in two distinct cohorts that shared the same inclusion criteria but used two different MOF definitions. Hutchings et al.¹⁹ reported MOF incidence in three distinct cohorts that shared the same inclusion criteria but used three different MOF definitions. Dewar et al.¹¹ reported MOF incidence in distinct four cohorts, which were created by the use of two different inclusion criteria and two different MOF definitions. Therefore, 113 distinct cohorts were identified from 106 included articles. The mean age of patients was 38 years, and 73% were male. The mean Injury Severity Score was 27.

Study Characteristics

There were 93 cohort studies, 3 secondary analyses of cohort studies, 3 randomized trials, 2 case control studies, 2 retrospective matched-pair analyses, 1 cross-sectional study, 1 prognostic study, and 1 pilot study.

TABLE 1. Summary of MOF Incidence by Subgroups Generated From MOF Definition and Study Population

MOF Definition	No. Cohorts	No. MOF Patients	No. Trauma Patients	Min % MOF	Max % MOF
Denver > 3	29	3,085	15,864	0.00	44.23
Unspecified	21	2,093	10,827	0.00	44.23
Blunt	8	992	5,037	9.07	31.16
Denver > 8 (Unspecified only)	4	63	257	16.56	46.15
Goris ≥ 4	5	262	1,516	13.73	73.02
Unspecified	2	55	76	69.23	73.02
Blunt	3	207	1,440	13.73	35.29
Goris ≥ 5 (Unspecified only)	6	450	2,451	6.03	56.13
Marshall > 5	18	4,084	10,576	8.10	71.43
Unspecified	3	734	1,957	34.56	71.43
Blunt	15	3,350	8,619	8.10	63.50
Marshall > 6	5	606	3,489	0.00	30.07
Unspecified	2	332	1,150	18.49	30.07
Blunt	3	274	2,339	0.00	29.37
Marshall > 8	5	138	1,387	7.07	12.95
Unspecified	4	102	1,109	7.07	7.42
Blunt	1	36	278	12.95	12.95
Marshall > 12 (Unspecified only)	4	85	991	5.29	16.78
SOFA > 3	3	108	185	37.50	61.36
Unspecified	1	3	8	37.50	37.50
Blunt	2	105	177	53.33	61.36
SOFA > 5	33	74,090	315,226	4.96	78.82
Unspecified	30	68,152	291,582	4.96	78.82
Blunt	3	5,938	23,644	23.57	51.90
TOTAL = 10 Definitions	113 cohorts (106 studies)	82,971	351,942	0.00	78.82

Max % MOF, highest percentage of MOF patients reported in a given subgroup; Min % MOF, lowest percentage of MOF patients reported in a given subgroup.

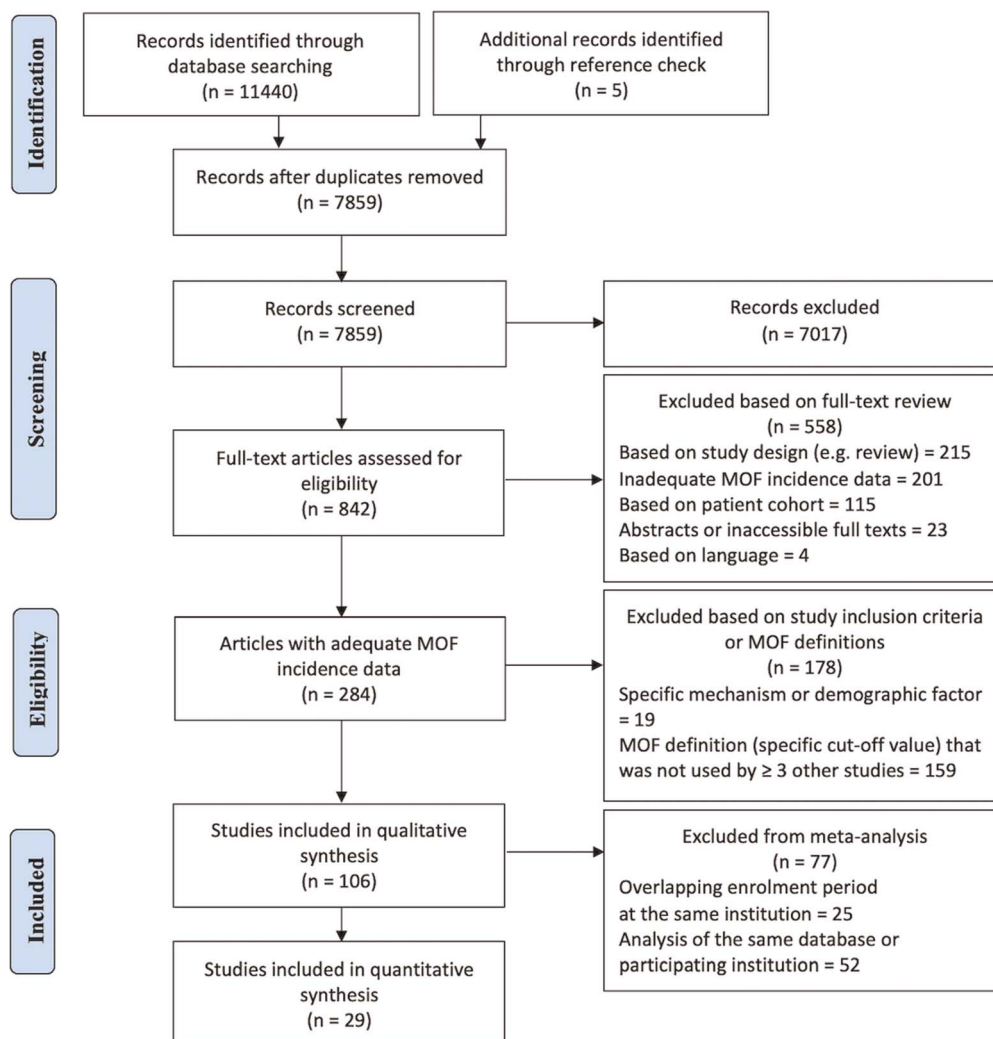


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flowchart outlining the study selection protocol.¹³

The quality appraisal of the studies indicated moderate to high quality of studies. There were 3 level 1 studies, 102 level 3 studies, and 1 level 4 study. Mixed Methods Appraisal Tool scores were 5/5 in 61 studies, 4/5 in 39 studies, and 3/5 in 6 studies. A supplement file shows this in more detail (Supplemental Digital Content, Supplementary Table 1, <http://links.lww.com/TA/C989>). We did not exclude any articles based on quality.

SYSTEMATIC REVIEW

MOF Definitions

Overall, 113 cohorts from 106 studies using 10 MOF definitions were included. Four scoring systems were used: Denver (three different cutoff values),^{4,7,9,18–43} Goris (two different cutoff values),^{5,44–53} Marshall (four different cutoff values),^{9,19,54–83} and Sequential Organ Failure Assessment (SOFA) (two different cutoff values).^{8,10,11,19,84–115} See Table 1.

Weighted Incidence of MOF by Publication Year

Included studies were published between 1992 and 2022. The weighted incidence of MOF from year to year ranged from 11% to 56% and fluctuated without significant change (Fig. 2).

META-ANALYSIS

Study Characteristics

There were 27 cohort studies and 2 randomized controlled trials. Publication years ranged from 1992 to 2022. A supplement file shows this in more detail (Supplemental Digital Content, Supplementary Table 2, <http://links.lww.com/TA/C990>).

Weighted Incidence of MOF by Definition and Study Population (Where Applicable)

Meta-analysis was performed in the following subgroups: Denver score >3, Denver score >3 with blunt injuries only, Denver score >8, Goris score ≥4, Marshall score >5, Marshall

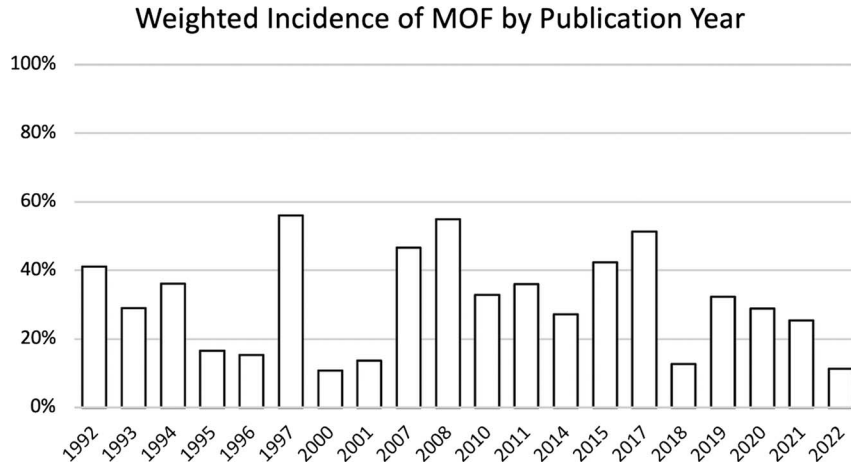


Figure 2. Weighted incidence of MOF based on publication year.

score >5 with blunt injuries only, SOFA score >3, SOFA score >3 with blunt injuries only, and SOFA score >5. The weighted incidences of MOF ranged from 12.7% to 55.1% (Fig. 3). A supplement file shows this in more detail (Supplemental Digital Content, Supplementary Fig. 1, <http://links.lww.com/TA/C991>).

DISCUSSION

This review was the largest of its kind and included more than 351,942 trauma patients over a 30-year period. The incidence of MOF varied from 0% to 79% within included studies, between 11% and 56% based on year of publication, and between 13% and 55% based on MOF definition and study population where applicable. Despite many authors suggesting that the incidence of MOF has decreased over time, the results of this review did not reveal any significant change over time.^{3,4,6,22,116-118} The large range of reported

incidence highlights one of the key challenges in researching MOF in trauma—a lack of a universally accepted definition.

The adult trauma population at risk for MOF represents a heterogeneous group.⁹⁻¹² We endeavored to minimize the heterogeneity and variation within the overall population (denominator) by only including studies whose individual inclusion criteria were similar to other included studies. However, there was still evidence of significant statistical heterogeneity. Because there is no universally preferred MOF definition, the included studies used 10 different threshold values from 4 major scoring systems to diagnose MOF.

Intuitively, a higher MOF threshold value from any of the scoring systems included should correspond with a decrease in incidence, provided the population at risk was the same. However, the incidence of MOF increased as the MOF cutoff value increased in our subgroup analysis of the Denver score, which

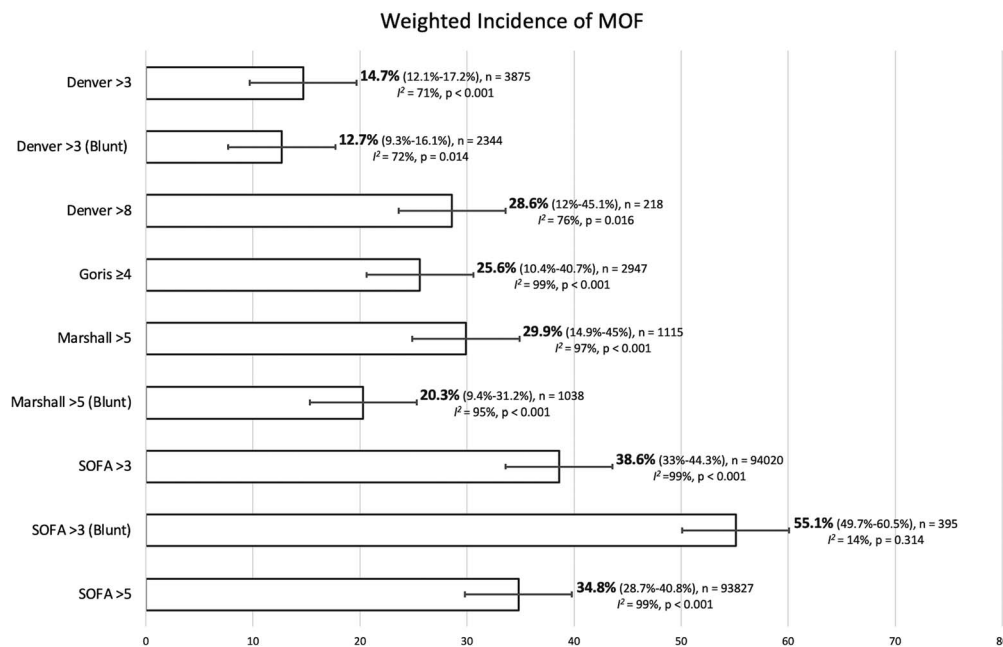


Figure 3. Weighted incidence of MOF based on MOF definitions and study population, where applicable. Data presented as weighted incidence (95% confidence interval), number of MOF patients/total number of trauma patients; I², p value.

is well validated in trauma patients. This suggests that there were fundamental differences study populations despite our efforts, and that the pooled samples with higher cutoff values (i.e., Denver score >8) were sicker than those with lower cutoff values (i.e., Denver score >3). This is critical to note because the literature does not compare apples with apples, and discussions about an accepted cutoff value for each scoring system need to factor this into consideration.

Hutchings et al.¹⁹ compared the incidence and predictive ability for mortality of postinjury MOF patients between the Denver, SOFA, and Marshall scoring systems and recommended the Denver score because it was simple to calculate, had the strongest association with early trauma mortality, and sensitively identified high risk patients.

The standout strength of this study is that it is the first study to examine the incidence of postinjury MOF in a systematic review format with the addition of meta-analysis. An intentionally broad search strategy, which included manuscripts in both English and German, was used to capture all published studies on this topic. Because of the inherent variation in the way individual studies defined the population at risk and therefore the resultant MOF incidence, an attempt to reduce this heterogeneity was made by way of including studies that shared inclusion criteria. However, there was still evidence of significant heterogeneity. All included studies were conducted in countries with developed health care and trauma systems, which may limit the external validity. Attempts to meta-analyze data were significantly impacted by overlapping recruitment between studies and highlight that, in the literature pool, the same patient is represented multiple times. Overall, the results clearly identified that the key impediment to MOF research in trauma cohorts is the lack of a universally accepted MOF definition, and this is the main limitation of the project and hinders future research on this critical area of trauma care research and management.

CONCLUSION

The literature pool on MOF in trauma cohorts is heterogeneous, both in the way authors define MOF and the study population at risk, and this limits any meaningful conclusion. There is no evidence to support a significant reduction in the incidence of MOF over the last 30 years, nor is there data to suggest what threshold values should be used for the various scoring systems. An international consensus is urgently needed on the definition of MOF using a scoring system that has been validated in trauma patients, with a specific cutoff value, and on the focused study population at risk of developing MOF.

AUTHORSHIP

R.S.T., P.S., L.D., and Z.J.B. performed the literature search. R.S.T., D.P.L., P.S., and Z.J.B. contributed to the study design. R.S.T., D.P.L., K.X.Y., T.A.N., P.S., L.D., S.H., K.K., C.L., M.S., W.R., H.A., and M.D. collected the data. R.S.T., D.P.L., and Z.J.B. curated the data and performed data analysis. All authors discussed and interpreted the data. R.S.T., D.P.L., and Z.J.B. drafted the manuscript. All authors critically revised and approved the final version of the manuscript. Z.J.B. supervised the study.

DISCLOSURE

The authors declare no conflicts of interest.

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