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Incidence of Multiple Organ Failure in Adult Polytrauma Patients: A Systematic Review and Meta-Analysis

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Social Media Summary: Urgent international consensus on the definition of MOF and the study population at risk is required to track its incidence and measure our efforts on its prevention and management. Without such a consensus, MOF will likely remain the lead cause of late death in trauma patients.

ABSTRACT

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 1977–2022 in English and German. Random effects meta-analysis was performed when applicable.

Results: The search returned 11440 results, of which 842 full-text articles were screened. MOF incidence was reported in 284 studies that used 11 unique inclusion criteria and 40 MOF definitions. 108 studies published from 1992-2018 were included. Weighted MOF incidence by publication year fluctuated from 11%-56% without significant decrease over time. MOF was defined using four scoring systems (Denver, Goris, Marshall, SOFA) and 12 different cut-off values. Overall, 353718 trauma patients were included, of whom 83766 (24%) developed MOF. The weighted incidences of MOF from meta-analysis of 30 eligible studies were: 14.7% (95% CI:12.1%-17.2%) in Denver>3, 12.7% (95% CI:9.3-16.1%) in Denver>3 with blunt injuries only, 28.6% (95% CI:12%-45.1%) in Denver>8, 25.6% (95% CI:10.4%-40.7%) in Goris>4, 29.9% (95% CI:14.9%-45%) in Marshall>5, 20.3% (95% CI:9.4%-31.2%) in Marshall>5 with blunt injuries only, 39.2% (95% CI:33.7%-44.7%) in SOFA>3, 47.3% (95% CI:29.1%-65.5%) in SOFA>4, 55.6% (95% CI:49.1%-62.2%) in SOFA>4 with blunt injuries only, 51.6% (95% CI:45.5%-57.7%) in SOFA>6.

Conclusions: The incidence of postinjury MOF varies largely due to lack of a consensus definition and study population. Until a consensus is reached, further research will be hindered.

Level of Evidence: Level III, Systematic Review and Meta-Analysis.

Keywords: Multiple Organ Failure; Polytrauma; Trauma; Shock; Systemic Inflammatory Response Syndrome

BACKGROUND

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 51-61% of late deaths in trauma patients, has become increasingly important (3, 4).

Whilst 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 disproportionally consumes healthcare resources. MOF cohorts in trauma have mean intensive care unit (ICU) 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 10-15% in those without (6, 7). Even amongst survivors of MOF, the long-term consequences are wide-reaching at a healthcare 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; both from a clinical and pathophysiological perspective. Knowledge derived from sepsis and other physiological insults have 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 cut-off 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 authors, 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 systemically 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.

METHODS

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (13) (Supplemental Digital Content, http://links.lww.com/TA/C881). The protocol was registered in The International Prospective Register of Systematic Reviews; PROSPERO ID: CRD42018095284.

Search Strategy

A systematic search was performed on 9 December 2022 using the Cochrane Library, EMBASE, MEDLINE, PubMed and Web of Science databases. Search terms were: ("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 onwards, when MOF was first described by Eiseman et al.(2)

The results returned by the search were exported to the EndNote X9 software (Clarivate Analytics, London, UK), 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 amongst 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, and healthcare systems, particularly emergency medical services, and advanced trauma care models, to those of Australia. Studies that focused on multiple organ dysfunction syndrome (MODS), 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 (SIRS) or acute respiratory distress syndrome (ARDS) without reference to MOF/MODS were excluded. Studies that concentrated on paediatric populations and non-mechanical 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.

Due to the inherent challenges of researching both polytraumatised patients and MOF due 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 was 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 haemorrhagic resuscitation etc.). Studies that did not specify a MOF scoring system and cut-off value, or had cohorts that used a MOF definition that was not used by ≥ 3 other cohorts, were excluded as 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 was extracted relating to demographic information of the patients, inclusion and exclusion criterion for each respective study, definitions of MOF, in addition to data on incidence, predictors and outcomes of MOF, 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, USA) was used to calculate the weighted incidence of MOF amongst included studies by publication year.

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

OpenMeta[Analyst] (CEBM, Brown University, RI, USA) 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% CI) amongst subgroups with different inclusion criteria and MOF definitions. A minimum of 3 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 (OCEBM) rating, and Mixed Methods Appraisal Tool (MMAT) (16, 17).

RESULTS

Study Selection

The initial search returned 11440 articles, of which 3581 were duplicates, resulting in a total of 7859 articles. Screening based on title and abstracts for relevance to MOF excluded 7017 articles, leaving 842 articles for full-text review. 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, 176 manuscripts were excluded due to 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. 19 studies comprising 55 cohorts were excluded as they focused on specific mechanism or demographic factors; penetrating mechanism (n=3 cohorts), < 65 years (n = 25 cohorts), age > 65 years (n = 4 cohorts), normal BMI (18.5-25 kg/m^2; n = 4 cohorts), overweight BMI (25-29.9 kg/m^2; n = 4 cohorts), obese BMI (30-39.9 kg/m^2; n = 7 cohorts), and morbidly obese BMI (>40 kg/m^2; n = 2 cohorts), alcohol intoxication (n = 3 cohorts), and no alcohol intoxication (n = 3 cohorts). A further 157 studies were excluded because the reported MOF definitions were not used by ≥ 3 other studies. Overall, 115 cohorts from 108 studies were included in the qualitative synthesis. A supplement file shows this in more detail [see Supplemental Digital Content 1, http://links.lww.com/TA/C882].

For meta-analysis, a further 25 studies were excluded because they had overlapping enrolment periods at the same institutions with another included study, and 53 studies because they had overlapping enrolment periods of analysis of the same database/participating institutions. Ultimately, 31 cohorts from 30 studies were included for quantitative synthesis (Figure 1).

Included Articles

Of the included studies, 4 of the 108 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 2 distinct cohorts that shared the same inclusion criteria, but used 2 different MOF definitions. Hutchings et al.(19) reported MOF incidence in 3 distinct cohorts that shared the same inclusion criteria, but used 3 different MOF definitions. Dewar et al.(11) reported MOF incidence in distinct 4 cohorts, which were created by the use of 2 different inclusion criteria, and 2 different MOF definitions. Therefore, 115 distinct cohorts were identified from 108 included articles. The mean age of patients was 38 years and 73% were male. The mean ISS was 27.

Study Characteristics

There were 95 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.

The quality appraisal of the studies indicated moderate to high quality of studies. There were three level 1 studies, one-hundred and four level 3 studies, and one level 4 study. MMAT scores were 5/5 in 63 studies, 4/5 in 39 studies, 3/5 in 6 studies. A supplement file shows this in more detail [see Supplemental Digital Content 1, http://links.lww.com/TA/C882]. We did not exclude any articles based on quality.

SYSTEMATIC REVIEW

MOF Definitions

Overall, 115 cohorts from 108 studies using 12 MOF definitions were included. Four scoring systems were used: Denver (3 different cut-off values)(4, 7, 9, 18-43), Goris (2 different cut-off values)(5, 44-53), Marshall (4 different cut-off values)(9, 19, 54-83), and SOFA (4 different cut-off values)(8, 10, 11, 84-118). 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 10% to 73%, and fluctuated without significant change (Figure 2).

META-ANALYSIS

Study Characteristics

There were 28 cohort studies and 2 randomized controlled trials. Publication years ranged from 1994-2022. A supplement file shows this in more detail [see Supplemental Digital Content 2, http://links.lww.com/TA/C883].

Weighted Incidence of MOF by Definition and Study Population (where applicable)

Meta-analysis was performed in the following subgroups: Denver >3, Denver >3 with blunt injuries only, Denver >8, Goris ≥4, Marshall >5, Marshall >5 with blunt injuries only, SOFA >3, and SOFA >4, SOFA >4 with blunt injuries only, and SOFA >6. The weighted incidences of MOF ranged from 12.7%-55.6% (Figure 3). A supplement file shows this in more detail [see Supplemental Digital Content 3, http://links.lww.com/TA/C884].

DISCUSSION

This review was the largest of its kind and included more than 353,718 trauma patients over a 30-year period. The incidence of MOF varied from 0% to 79% within included studies, and between 11% and 56% based on year of publication. Despite many authors suggesting the incidence of MOF has decreased over time, the results of this review did not support any significant change over time (3, 4, 6, 22, 119-121). 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 heterogenous group (9-12). We endeavoured to minimise the heterogeneity and variation within the overall population (denominator) by only including studies whose individual inclusion criteria were similar to other included studies. Although, there was still evidence of significant statistical heterogeneity. As there is no universally preferred MOF definition, the included studies used 12 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 cut-off value increased in our subgroup analysis. This suggests that there were fundamental differences in the population despite our efforts, and that the pooled samples with higher cut-off values (i.e. Denver >8) were sicker than those with lower cut-off values (i.e. Denver >3). Furthermore, studies with mixed injury mechanism patients reported a higher incidence of MOF than studies that exclusively reported on blunt trauma. This suggest that penetrating trauma might be associated with higher incidence of MOF, which needs to be confirmed by quality prospective studies on this topic. This is critical to note as the literature does not compare apples with apples, and discussions about an accepted cut off value for each scoring system need to factor this into consideration.

The Denver and Goris scores were the most frequently used scoring systems amongst included studies. However, Denver >3 was the single most frequently reported MOF definition, likely due to more recent literature validating its use in the trauma cohort (108, 121). The Marshall score had the greatest variation in cut-off values for the diagnosis of MOF, which ranged from >6 to >12. Hutchings et al.(108) 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. However, the number of studies identified during the search resulted in a delay between the search date and publication. Due to 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 and the incidence of MOF increased with higher MOF threshold values for each scoring system, which should not be the case. All included studies were conducted in countries with developed healthcare and trauma systems, which may limit the external validity. Attempts to meta-analyse data were significantly impacted by overlapping recruitment between studies, and highlights 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.

CONCLUSIONS

The literature pool on MOF in trauma cohorts is heterogenous, both in the way authors define MOF and the 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 what constitutes MOF in trauma

patients, including the definition of MOF, the suggested scoring systems to be used, as well as the threshold required to diagnose MOF.

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FIGURE LEGENDS

Figure 1. PRISMA Flowchart outlining the study selection protocol (13).

Figure 2. Weighted incidence of MOF (95% CI) based on publication year.

Figure 3. Weighted incidence of MOF based on MOF definitions and study population, where applicable. Data presented as weighted incidence (95% CI), number of MOF patients/total number of trauma patients; I^2, p-value

Supplemental Digital Content (SDC)

SDC 1. Summary table of included studies.

SDC 2. Summary table of studies included in meta-analysis.

SDC 3. Forest plots of comparison for MOF incidence based on cut-off values and study populations, where applicable.

Figure 1

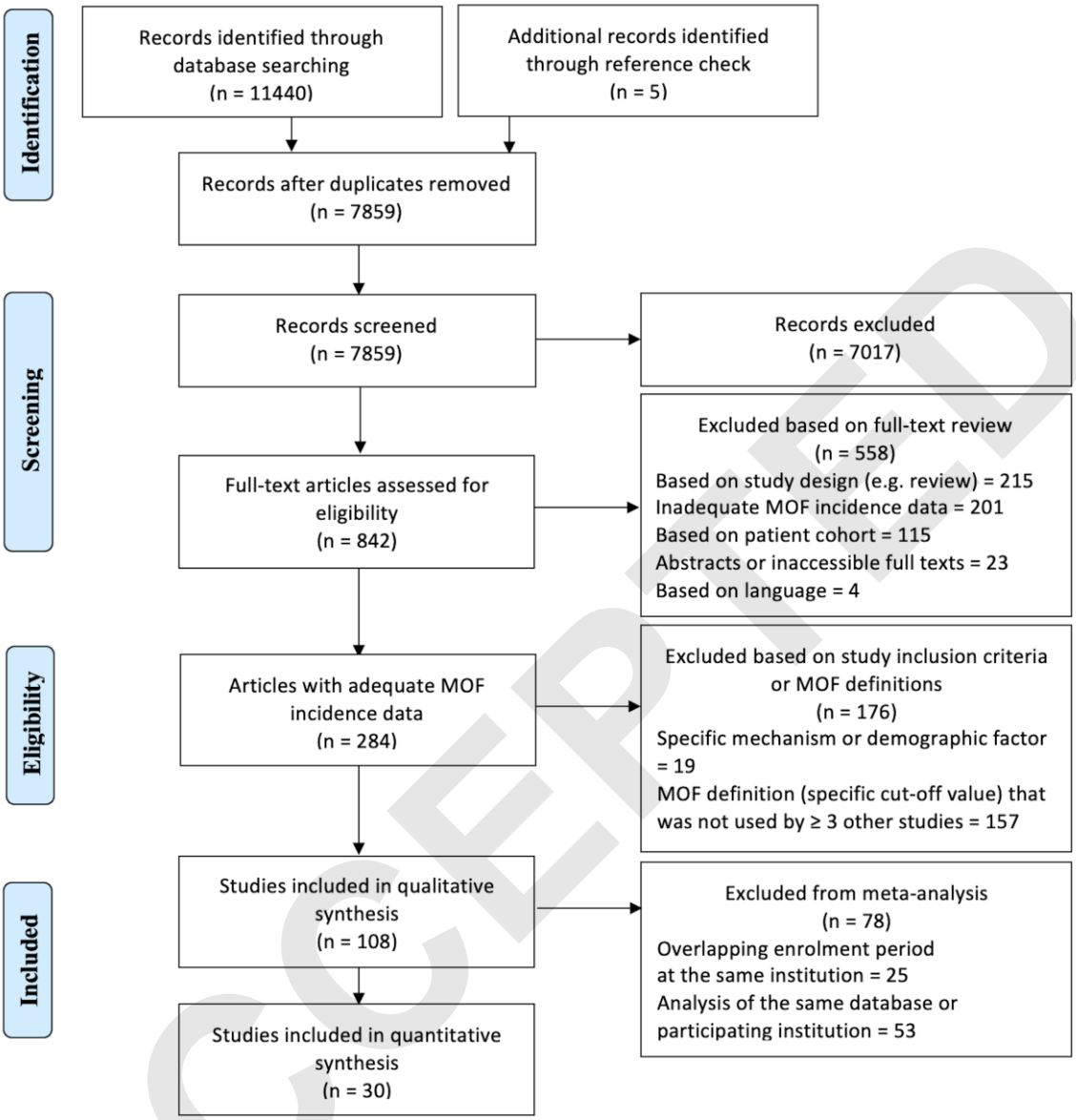

Figure 2

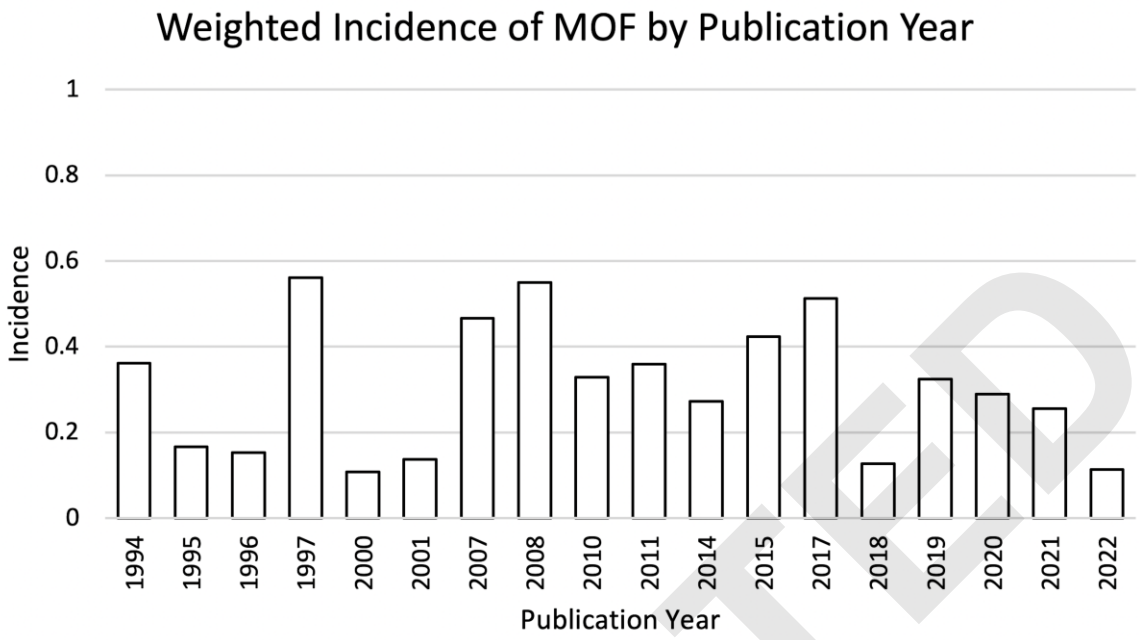

Figure 3

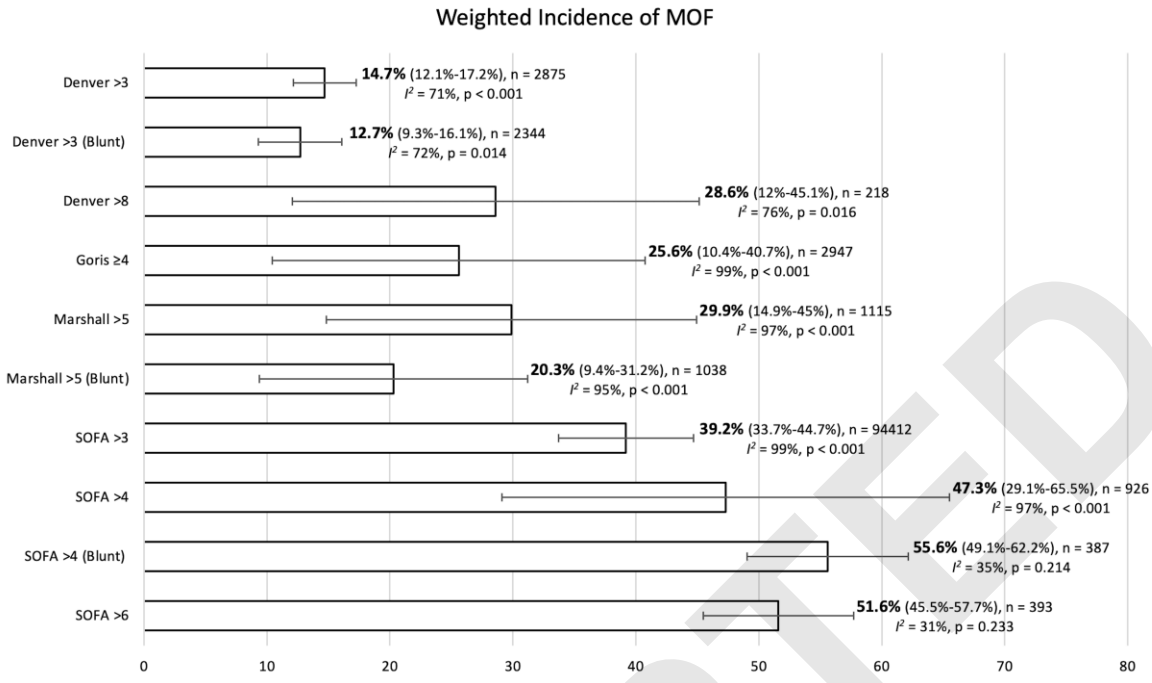

Table 1. Summary of MOF incidence by subgroups generated from MOF definition and study population.

MOF Definition	# Cohorts	# MOF Patients	# Trauma patients	Min % MOF	Max % MOF
Denver >3	29	3085	15864	0.00%	44.23%
Unspecified	21	2093	10827	0.00%	44.23%
Blunt	8	992	5037	9.07%	31.16%
Denver >8 (Unspecified only)	4	63	257	16.56%	46.15%
Goris ≥4	5	262	1516	13.73%	73.02%
Unspecified	2	55	76	69.23%	73.02%
Blunt	3	207	1440	13.73%	35.29%
Goris ≥ 5 (Unspecified only)	6	450	2451	6.03%	56.13%
Marshall >5	18	4084	10576	8.10%	71.43%
Unspecified	3	734	1957	34.56%	71.43%
Blunt	15	3350	8619	8.10%	63.50%
Marshall >6	5	606	3489	0.00%	30.07%
Unspecified	2	332	1150	18.49%	30.07%
Blunt	3	274	2339	0.00%	29.37%
Marshall >8	5	138	1387	7.07%	12.95%
Unspecified	4	102	1109	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	17	41577	193703	4.96%	55.00%
Unspecified	16	38186	180612	4.96%	55.00%
Blunt	1	3391	13091	25.90%	25.90%
SOFA >4	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	3	772	1122	44.44%	78.82%
Unspecified	2	756	1086	58.45%	78.82%
Blunt	1	16	36	44.44%	44.44%
SOFA >6	16	32546	122177	5.79%	57.73%
Unspecified	14	29999	111624	5.79%	57.73%
Blunt	2	2547	10553	23.57%	51.90%
TOTAL = 12 Definitions	115 cohorts (108 studies)	83766	353718	0.00%	78.82%

#, number of

Min % MOF, lowest percentage of MOF patients reported in a given subgroup

Max % MOF, highest percentage of MOF patients reported in a given subgroup

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title and Abstract
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 1
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 1-2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 3-4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 3-4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the	Page 5-6

Section and Topic	Item #	Checklist item	Location where item is reported
		model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 5-6
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 5-6
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 7
Study characteristics	17	Cite each included study and present its characteristics.	Page 8, Supplemental Digital Content 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	N/A
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Supplemental Digital Content 1 Supplemental Digital Content 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Supplemental Digital Content 1 Supplemental Digital Content 2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 9-10 Figure 2, Figure 3
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 9,

Section and Topic	Item #	Checklist item	Location where item is reported
			Figure 3
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 9-10, Figure 2, Figure 3
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 11-12
	23b	Discuss any limitations of the evidence included in the review.	Page 11-12
	23c	Discuss any limitations of the review processes used.	Page 12
	23d	Discuss implications of the results for practice, policy, and future research.	Page 13
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	No funding was received for this study. Declared on title page per author guidelines
Competing interests	26	Declare any competing interests of review authors.	The authors declare no conflict of interest. Declared on title page per author guidelines
Availability of data, code and	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

Section and Topic	Item #	Checklist item	Location where item is reported
other materials			

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Supplemental Digital Content 1. Summary table of included studies.

Study ID	Country	Institution (Database)	Data Collection Period	Inclusion Criteria	Study Population	Mean Age (SD)	Males (%)	Mean ISS (SD)	MOF Definition	# Trauma Patients	# MOF Patients	Incidence	OCEBM	MMAT Score
Balogh 2000(1)	USA	Denver Health Medical Center (IHRI)	1992-1998	Age > 15 ISS > 15 Survival > 48 hrs	Unspecified Mechanism	36 (0.7)	-	27 (0.4)	Denver> 3	558	101	18.10%	3	5
Ciesla 2005(2)	USA	Denver Health Medical Center (IHRI)	1991-2003	Age > 15 ISS > 15 Survival > 48 hrs ICU admission	Unspecified Mechanism	37	73%	29	Denver> 3	1344	339	25.22%	3	5
Ciesla 2006(3)	USA	Denver Health Medical Center (IHRI)	1998-2004	Age > 15 ISS > 15 Survival > 48 hrs SICU admission within 24 hrs of injury	Unspecified Mechanism	39	71	31	Denver> 3	716	179	25.00%	3	5
Dewar 2009(4)	Australia	John Hunter Hospital	2005	Age > 18 ISS > 15 Head AIS < 3 Survival > 48 hrs	Blunt Mechanism	40 (4)	62%	-	Denver> 3	28	5	17.86%	3	5
Dewar 2013(5)	Australia	John Hunter Hospital	2005-2010	Age > 18 ISS > 15 Head AIS < 3 ICU admission Survival > 48 hrs	Unspecified Mechanism	47	69	30	Denver> 3	140	21	15.00%	3	4
Dewar 2014(6)[a]	Australia	John Hunter Hospital	2005-2010	Age > 18 ISS > 15	Unspecified Mechanism	47 (21)	69	30 (11)	Denver> 3	8	0	0.00%	3	5
					Unspecified Mechanism				SOFA≥4	8	3	37.50%		
					Blunt Mechanism				Denver >3	132	21	15.91%		
					Blunt Mechanism				SOFA≥4	132	81	61.36%		
Giles 2022(7)	Australia	John Hunter Hospital	2012-2019	Age > 16 ISS > 15	Unspecified trauma	45 (19)	75	Median 25 (20, 34)	Denver> 3	663	75	11.31%	3	5

Study ID	Country	Institution (Database)	Data Collection Period	Inclusion Criteria	Study Population	Mean Age (SD)	Males (%)	Mean ISS (SD)	MOF Definition	# Trauma Patients	# MOF Patients	Incidence	OCEBM	MMAT Score
Harr 2013(8)	USA	IHRI Database Study	2001-2008	Blunt trauma Age > 45 ED base deficit > 6 mEq/L or systolic blood pressure < 90 mmHg ED arrival within 6 hrs of injury	Blunt Mechanism	-	64%	-	Denver> 3	839	151	18.00%	3	4
Haupt 2021(9)	Germany	University Hospital of Munich (TR-DGU)	1 year period, dates not specified	Age > 18 ISS ≥ 16	Unspecified trauma	50	57	Median 41	Denver> 3	28	4	14.29%	3	5
Hesselink 2019(10)	Netherlands	University Medical Center Utrecht	2007-2013	Age ≥ 16 ISS > 16 Femur fracture	Unspecified trauma	-	77	-	Denver> 3	81	4	4.94%	3	4
Hutchings 2017(11)[a]	UK	John Radcliffe Hospital (TARN)	2003-2011	Age > 18 ICU admission	Unspecified Mechanism	38	76%	25	Denver> 3	491	112	22.81%	3	4
									Marshall >5	491	199	40.53%		
									SOFA≥5	491	287	58.45%		
Johnson 2010(12)	USA	Denver Health Medical Center (IHRI)	1992-2004	ISS > 15 Survival > 48 hrs ICU admission within 12 hrs of injury	Unspecified Mechanism	37	72%	29	Denver> 3	1440	346	24.03%	3	4
Kornblith 2015(13)	USA	University of California, San Francisco, USA (IHRI)	2005-2013	BMI ≥ 18.5	Unspecified Mechanism	33	81%	18	Denver> 3	377	34	9.02%	3	3
Kutcher 2013(14)	USA	University of California, San Francisco (IHRI)	2005-2010	Local criteria for full trauma team activation	Unspecified Mechanism	41 (19)	-	23 (5)	Denver> 3	163	41	25.15%	3	5
Kutcher 2015(15)	USA	IHRI Database Study	2003-2011	Blunt trauma Hemorrhagic shock (base	Blunt Mechanism	43 (18)	66%	33 (14)	Denver> 3	1537	479	31.16%	3	3

Study ID	Country	Institution (Database)	Data Collection Period	Inclusion Criteria	Study Population	Mean Age (SD)	Males (%)	Mean ISS (SD)	MOF Definition	# Trauma Patients	# MOF Patients	Incidence	OCEBM	MMAT Score
				deficit > 6 mEq/L or systolic blood pressure < 90 mmHg) Blood transfusion within 12 hrs of admission										
Lumsdaine 2014(16)	Australia	John Hunter Hospital	2011-2012	Age >16 Pelvic, acetabular, femoral shaft or tibial shaft fractures requiring surgical intervention	Unspecified Mechanism	42	78%	19 (13)	Denver> 3	100	11	11.00%	3	5
Moore 1996(17)	USA	Denver Health Medical Center (IHRI)	1991-1994	Age > 16 ISS > 15 Survival > 48 hrs ICU admission	Unspecified Mechanism	36 (0.7)	77%	25 (0.4)	Denver> 3	457	70	15.32%	3	5
Moore 2009(18)	USA	Multicenter Study (29 Level I Trauma Centers; IHRI)	2004-2006	Age > 18 Class III hemorrhagic shock	Unspecified Mechanism	37	79%	20 (13)	Denver> 3	714	46	6.44%	1	5
Nydam 2011(19)	USA	Denver Health Medical Center (IHRI)	1992-2004	ISS > 15 Survival > 48 hrs ICU admission within 12 hrs of injury	Unspecified Mechanism	37 (17)	72%	29 (11)	Denver> 3	1415	346	24.45%	3	5
Offner 2001(20)	USA	Denver Health Medical Center (IHRI)	1994-1999	Age > 15 ISS > 15 Survival > 48 hrs	Unspecified Mechanism	33	73%	28	Denver> 3	52	23	44.23%	3	4
Peerless 2000(21)	USA	MetroHealth Medical Center	Not specified	Blunt trauma Age ≥ 18 ISS > 15 Mechanically ventilated	Blunt Mechanism	50 (19)	66%	31 (11)	Denver> 3	62	10	16.13%	3	5

Study ID	Country	Institution (Database)	Data Collection Period	Inclusion Criteria	Study Population	Mean Age (SD)	Males (%)	Mean ISS (SD)	MOF Definition	# Trauma Patients	# MOF Patients	Incidence	OCEBM	MMAT Score
Richards 2018(22)	USA	University of Maryland Medical Center	2010-2014	Blunt trauma Age ≥ 18 ISS > 15 Head AIS < 3 ICU admission	Blunt Mechanism	45 (18)	61%	Median 27 (21, 34)	Denver> 3	507	46	9.07%	3	4
Sauaia 1993(23)	USA	Denver Health Medical Center (IHRI)	1990-1992	ISS > 15 Required > 24 hrs mechanical ventilation Torso injuries SICU admission	Unspecified Mechanism	36	78%	26	Denver> 3	123	28	22.76%	3	4
Sauaia 1998(24)[a]	USA	Denver Health Medical Center (IHRI)	1992-1995	Age > 15 ISS > 15 Admission within 24 hrs of injury	Unspecified Mechanism	36	76%	-	Denver> 3	411	78	18.98%	3	4
					Blunt Mechanism				Denver> 3	289	57	19.72%		
Sauaia 2009(25)[a]	USA	Denver Health Medical Center (IHRI)	1992-2004	Age > 15 ISS ≥ 15 Survival > 48 hrs Admission to the SICU within 24 hours of injury	Unspecified Mechanism	36	72%	30	Marshall >5	1389	480	34.56%	3	4
									Denver> 3	1389	204	14.69%		
Sauaia 2014(26)	USA	IHRI Database Study	2003-2010	Blunt trauma Torso Age 16-90 ED arrival < 6 hrs postinjury Blood product transfusion within 12 hrs of ED arrival	Blunt Mechanism	27	65-68%	29-34	Denver> 3	1643	223	13.57%	3	4
Van Wessem 2018(27)	Netherlands	University Medical Center Utrecht	2013-2016	ICU Admission	Unspecified Mechanism	Median 45	75%	Median 29	Denver> 3	157	31	19.75%	3	4
Law 1994(28)	USA	UCLA Medical Center, USA	1991-1992	Age ≥ 18	Unspecified Mechanism	45	85%	38	Denver> 8	13	6	46.15%	3	4

Study ID	Country	Institution (Database)	Data Collection Period	Inclusion Criteria	Study Population	Mean Age (SD)	Males (%)	Mean ISS (SD)	MOF Definition	# Trauma Patients	# MOF Patients	Incidence	OCEBM	MMAT Score
Moore 1992(29)	USA	Hannover Medical School, Germany (TR-DGU)	1991-1992	Major trauma patients with any of the following; major abdominal trauma, massive transfusion > 10 units in 24hrs, flail chest with pulmonary contusions, multiple fractures require blood transfusion and had a pulmonary wedge catheter	Unspecified Mechanism	36	83%	31	Denver> 8	39	16	41.03%	3	5
Smail 1995(30)	France	Bicêtre Hospital	1989-1991	Trauma patients requiring ICU care	Unspecified Mechanism	39 (18)	76%	33 (14)	Denver> 8	163	27	16.56%	3	4
Svoboda 1994(31)	Czech Republic	The Research Institute for Traumatology and Special Surgery, Czechoslovakia	1992	ISS ≥ 16	Unspecified Mechanism	47 (21)	55%	29	Denver> 8	42	14	33.33%	3	5
Bogner 2007(32)	Germany	Ludwig-Maximulians University (TR-DGU)	Not specified	Age > 18 ISS >16 reached ED within 90 minutes of injury	Unspecified Mechanism	-	85%	40	Goris≥4	13	9	69.23%	3	5
Nast-Kolb 2001(33)	Germany	Universitätsklinikum Essen	1975-1990	ISS ≥ 16	Blunt Mechanism	33-40	68-80%	28-31	Goris≥4	1361	187	13.74%	3	4
Roumen 1993(34)	Austria & The Netherlands	Lorenz Bohler Hospital, Austria; University of Innsbruck, Austria; University Hospital Nijimegan, Netherlands;	Not specified	Blunt trauma ISS ≥ 33	Blunt Mechanism	33 (range 14-71)	82%	45 (29)	Goris≥4	51	18	35.29%	3	5

Study ID	Country	Institution (Database)	Data Collection Period	Inclusion Criteria	Study Population	Mean Age (SD)	Males (%)	Mean ISS (SD)	MOF Definition	# Trauma Patients	# MOF Patients	Incidence	OCEBM	MMAT Score
Roumen 1994(35)	Netherlands	University of Innsbruck	Not specified	ISS > 25 ICU Hemorrhagic shock after ruptured abdominal aortic aneurysm	Blunt Mechanism	31 (14)	79%	38 (11)	Goris≥4	28	2	7.14%	3	5
von Heymann 2002(36)	Germany	Universitätsklinikum Charité Campus Mitte, Humboldt-University (TR-DGU)	Not specified	trauma patients in the ICU were enrolled into this study	Unspecified Mechanism	-	84%	-	Goris≥4	63	46	73.02%	3	3
Kerner 1999(37)	Germany	Charite Virchow Hospital, (TR-DGU)	2 year period, dates not specified	ISS > 16	Unspecified Mechanism	Median 32	78%	Median 29	Goris≥5	51	26	50.98%	3	5
Lingnau 1997(38)	Austria	University of Innsbruck	1989-1994	Age > 18 ISS ≥ 16 NO antibiotic pretreatment/infection history ICU admission	Unspecified Mechanism	38	78%	35	Goris≥5	310	174	56.13%	1	5
Lustenberger 2016(39)	Germany	University Hospital of the Goethe University Frankfurt (TR-DGU)	2007-2008	Age 18-80 ISS ≥ 16 Blunt or Penetrating Trauma	Unspecified Mechanism	46 (2)	78%	30	Goris≥5	123	18	14.63%	3	4
Maier 2007(40)	Germany	University Clinics in Cologne and Homburg/Saar (TR-DGU)	1998-2000	Age ≥ 16 Severe Traumatic brain injury (GCS ≤ 8 or distinct cranial changes on CT)	Unspecified Mechanism	-	78%	-	Goris≥5	352	53	15.06%	3	5
Oberholzer 2000(41)	Switzerland	University Hospital Zurich	1991-1996	Age > 16 ISS ≥ 9 Admission < 4 hrs from Injury Survival > 3 days	Unspecified Mechanism	41 (2)	71%	19 (8)	Goris≥5	1276	102	7.99%	3	5

Study ID	Country	Institution (Database)	Data Collection Period	Inclusion Criteria	Study Population	Mean Age (SD)	Males (%)	Mean ISS (SD)	MOF Definition	# Trauma Patients	# MOF Patients	Incidence	OCEBM	MMAT Score
Wanner 2000(42)	Switzerland	University Hospital Zurich	1994-1996	Age > 16 ISS ≥ 9 Admission < 4 hrs from Injury Survival > 3 days	Unspecified Mechanism	40	74%	23	Goris≥5	339	77	22.71%	3	5
Andruszkow 2013(43)	Germany	University Hospital Aachen (TR-DGU)	2005-2011	Age ≥ 16 ISS ≥ 16 ICU admission within 24 hrs	Unspecified Mechanism	42 (18)	70%	29 (11)	Marshall >12	586	31	5.29%	3	5
Andruszkow 2013(44)	Australia & Germany	The Alfred Hospital, Australia; University Hospital Aachen (TR-DGU), Germany	2003-2007	Age ≥ 16 ISS ≥ 16 Femoral Shaft Fracture	Unspecified Mechanism	35 (16)	68%	-	Marshall >12	207	23	11.11%	3	4
Frink 2009(45)	Germany	Hannover Medical School (TR-DGU)	1997-2001	Polytrauma; Age 16-65	Unspecified Mechanism	37	74%	25	Marshall >12	143	24	16.78%	3	5
Mommsen 2009(46)	Germany	Hannover Medical School (TR-DGU)	2005	Polytrauma; Admission within 6 hrs of injury > 48 hrs survival in ICU	Unspecified Mechanism	33 (13)	75%	28 (13)	Marshall >12	55	7	12.73%	3	5
Edmonds 2011(47)	USA	University of Pittsburgh Medical Center	2003	Blunt trauma Base deficit ≥ 6 mEq/L or systolic blood pressure < 90 mmHg Blood transfusion in first 12 hrs AIS ≥ 2 (except for head)	Blunt Mechanism	41 (19)	64%	32 (14)	Marshall >5	820	300	36.59%	3	5
Kasotakis 2019(48)	USA	IHRI Database Study	Not specified	Blunt trauma Age > 18 and < 90 ED arrival within 6 hrs of injury	Blunt trauma	44 (20)	66	33 (13)	Marshall >5	488	158	32.38%	3	5
Neal 2009(49)	USA	University of Pittsburgh Medical	2003-2007	Blunt trauma Base deficit ≥ 6	Blunt Mechanism	Median 66	69%	Median 29 (21,	Marshall >5	295	148	50.17%	3	5

Study ID	Country	Institution (Database)	Data Collection Period	Inclusion Criteria	Study Population	Mean Age (SD)	Males (%)	Mean ISS (SD)	MOF Definition	# Trauma Patients	# MOF Patients	Incidence	OCEBM	MMAT Score
		Center		mEq/L or systolic blood pressure < 90 mmHg Blood transfusion in first 12 hrs AIS ≥ 2 (except for head)		(58, 76)		41)						
Neal 2012(50)	USA	University of Pittsburgh Medical Center	2003-2008	Blunt trauma Base deficit ≥ 6 mEq/L or systolic blood pressure < 90 mmHg Blood transfusion in first 12 hrs AIS ≥ 2 (except for head)	Blunt Mechanism	41 (17)	70%	Median 34	Marshall >5	452	287	63.50%	3	5
Peralta 2015(51)	Qatar	Hamad General Hospital	2010-2012	Massive Transfusion Protocol (≥ 10 units) during first 24 hrs postinjury	Unspecified Mechanism	34 (1)	91%	Median 29 (8, 75)	Marshall >5	77	55	71.43%	3	3
Scannell 2010(52)	USA	Carolinas Medical Center	2001-2007	Blunt trauma ISS ≥ 17 Femoral shaft fracture treated with intramedullary nail	Blunt Mechanism	31 (15)	66%	26 (8)	Marshall >5	205	53	25.85%	3	4
Sperry 2007(53)	USA	IHRI Database Study	2003-2006	Blunt trauma Base deficit ≥ 6 mEq/L or systolic blood pressure < 90 mmHg Blood transfusion in first 12 hrs AIS ≥ 2 (except	Blunt Mechanism	40	65%	32	Marshall >5	850	167	19.65%	3	4

Study ID	Country	Institution (Database)	Data Collection Period	Inclusion Criteria	Study Population	Mean Age (SD)	Males (%)	Mean ISS (SD)	MOF Definition	# Trauma Patients	# MOF Patients	Incidence	OCEBM	MMAT Score
				for head)										
Sperry 2008(54)	USA	IHRI Database Study	2003-2007	Blunt trauma Base deficit ≥ 6 mEq/L or systolic blood pressure < 90 mmHg Blood transfusion in first 12 hrs AIS ≥ 2 (except for head)	Blunt Mechanism	41 (18)	66%	32 (14)	Marshall >5	1036	416	40.15%	3	4
Sperry 2008(55)	USA	IHRI Database Study	2003-2007	Blunt trauma Base deficit ≥ 6 mEq/L or systolic blood pressure < 90 mmHg Blood transfusion in first 12 hrs AIS ≥ 2 (except for head)	Blunt Mechanism	33	58%	31	Marshall >5	80	27	33.75%	3	5
Sperry 2008(56)	USA	IHRI Database Study	2003-2007	Blunt trauma Base deficit ≥ 6 mEq/L or systolic blood pressure < 90 mmHg Blood transfusion in first 12 hrs AIS ≥ 2 (except for head)	Blunt Mechanism	41	70%	Median 34 (22-43)	Marshall >5	415	234	56.39%	3	5
Sperry 2009(57)	USA	IHRI Database Study	2003-2007	Blunt trauma Base deficit ≥ 6 mEq/L or systolic blood pressure < 90 mmHg Blood transfusion in first 12 hrs AIS ≥ 2 (except	Blunt Mechanism	42 (18)	65%	32 (13)	Marshall >5	862	306	35.50%	3	4

Study ID	Country	Institution (Database)	Data Collection Period	Inclusion Criteria	Study Population	Mean Age (SD)	Males (%)	Mean ISS (SD)	MOF Definition	# Trauma Patients	# MOF Patients	Incidence	OCEBM	MMAT Score
				for head)										
Sperry 2014(58)	USA	IHRI Database Study	2011-2012	Blunt trauma Age > 17 ICU admission	Blunt Mechanism	50 (16)	70%	Median 16 (10-21)	Marshall >5	321	26	8.10%	3	5
Watson 2009(59)	USA	University of Pittsburgh Medical Center	2003-2007	Blunt trauma Base deficit ≥ 6 mEq/L or systolic blood pressure < 90 mmHg Blood transfusion in first 12 hrs AIS ≥ 2 (except for head) Survival > 48 h	Blunt Mechanism	Media n 41	64%	Median 32	Marshall >5	1175	482	41.02%	3	5
Winfield 2010(60)	USA	IHRI Database Study	2001-2008	Blunt trauma Age > 16 Base deficit ≥ 6 mEq/L or systolic blood pressure < 90 mmHg	Blunt Mechanism	-	65%	-	Marshall >5	877	480	54.73%	4	5
Winfield 2010(61)	USA	IHRI Database Study	2001-2008	Blunt trauma Age 16-55 Base deficit ≥ 6 mEq/L or systolic blood pressure < 90 mmHg AIS > 2 (except for head) Blood transfusion within 12 hrs of injury	Blunt Mechanism	-	64%	-	Marshall >5	455	227	49.89%	4	4
Zolin 2015(62)	USA	University of Pittsburgh Medical Center	2011-2012	Blunt trauma Age ≥ 17 ICU admission Admission within	Blunt Mechanism	50 (18)	69	Median 16 (10, 21)	Marshall >5	288	39	13.54%	3	4

Study ID	Country	Institution (Database)	Data Collection Period	Inclusion Criteria	Study Population	Mean Age (SD)	Males (%)	Mean ISS (SD)	MOF Definition	# Trauma Patients	# MOF Patients	Incidence	OCEBM	MMAT Score
				6 hrs of injury										
Brakenridge 2011(63)	USA	University of Texas Southwestern Medical Center	Not specified	Blunt trauma Base deficit ≥ 6 mEq/L or systolic blood pressure < 90 mmHg AIS > 2 (except for head) Blood transfusion within 12 hrs of injur	Blunt Mechanism	Median 41 (26, 54)	-	-	Marshall >6	1366	0	0.00%	3	5
Minei 2012(64)	USA	IHRI Database Study	2003-2007	Blunt trauma Base deficit ≥ 6 mEq/L or systolic blood pressure < 90 mmHg AIS > 2 (except for head)	Blunt Mechanism	Median 40 (26, 54)	65%	Median 29 (22, 41)	Marshall >6	916	269	29.37%	3	5
Peltan 2015(65)	USA	University of Washington Medical Center (USA)	2003-2010	Base Deficit ≥ 6 mEq/L or Systolic Blood Pressure < 90 mmHg within 60 minutes of ED arrival non-head AIS ≥ 2 Required red blood cell transfusion within 12 hours	Unspecified Mechanism	41	67%	33	Marshall >6	1031	310	30.07%	3	3
Schroder 2004(66)	Germany	Unfallkrankenhaus Berlin (TR-DGU)	2002-2003	ISS ≥ 15 ≥ 1 life threatening injury ≥ 1 severe injury in another body part	Unspecified Mechanism	34 (17)	77%	38 (13)	Marshall >6	119	22	18.49%	3	5

Study ID	Country	Institution (Database)	Data Collection Period	Inclusion Criteria	Study Population	Mean Age (SD)	Males (%)	Mean ISS (SD)	MOF Definition	# Trauma Patients	# MOF Patients	Incidence	OCEBM	MMAT Score
Wang 2014(67)	China	Chongqing Medical University	2011-2012	Blunt trauma AIS Chest ≥ 3 Admission within 24 hrs of injury Survival > 7 days	Blunt Mechanism	44 (13)	72%	17 (6)	Marshall >6	57	5	8.77%	3	5
Leditzke 2021(68)	Germany	Hannover Medical School (TR-DGU)	4 year period, dates not specified	ISS ≥ 16 Complete plasma samples	Unspecified trauma	41 (20)	82	34 (11)	Marshall >8	39	14	35.90%	3	5
Mommsen 2012(69)	Germany	Hannover Medical School (TR-DGU)	2000-2009	Blunt trauma Age > 16 ISS ≥ 16 AIS Chest ≥ 3 AIS Head ≥ 2 Admission within 6 hrs of injury Survival ≥ 48 hrs	Blunt Mechanism	43 (17)	73%	29 (9)	Marshall >8	278	36	12.95%	3	5
Mommsen 2013(70)	Germany	Hannover Medical School (TR-DGU)	2005-2009	Age ≥ 16 ISS ≥ 16 Admission within 6 hrs of injury Temperature recorded within 2 hrs of injury	Unspecified Mechanism	42 (18)	71%	30 (10)	Marshall >8	310	23	7.42%	3	5
Omar 2018(71)	Germany	Hannover Medical School (TR-DGU)	2005-2014	Age > 14 ISS ≥ 16 ICU admission within 72 hrs of trauma	Unspecified Mechanism	42 (19)	72%	30 (10)	Marshall >8	721	51	7.07%	3	4
Peters 2019(72)	Germany	Hannover Medical School (TR-DGU)	2009-2012	Age ≥ 16 ISS ≥ 16 ED arrival < 6 hrs postinjury	Unspecified trauma	41 (20)	82	32 (11)	Marshall >8	39	14	35.90%	3	5
Andruszkow 2013(73)	Germany	University Hospital Aachen (TR-DGU)	2007-2009	Age≥ 16 ISS ≥ 16 ICU Admission within 24 hrs of	Unspecified Mechanism	-	71%	-	SOFA≥3	13220	3742	28.31%	3	4

Study ID	Country	Institution (Database)	Data Collection Period	Inclusion Criteria	Study Population	Mean Age (SD)	Males (%)	Mean ISS (SD)	MOF Definition	# Trauma Patients	# MOF Patients	Incidence	OCEBM	MMAT Score
				injury										
Ballesteros 2022(74)	Spain	RETRAUCI Database Study	2015-2019	Age > 18 Survival > 48 hrs post-injury	Unspecified trauma	49 (19)	77	19 (11)	SOFA≥3	9282	750	8.08%	3	5
Barea-Mendoza 2021(75)	Spain	RETRAUCI Database Study	2015-2019	Age > 18	Unspecified trauma	50 (19)	78	20 (12)	SOFA≥3	9598	965	10.05%	3	5
Blasius 2022(76)	Germany	University Hospital Aachen (TR-DGU)	2002-2018	Blunt trauma Age ≥ 16 ISS ≥ 9 Maximum AIS ≥ 3 Femur fracture	Blunt trauma	44 (21)	72	23 (13)	SOFA≥3	13091	3391	25.90%	3	5
Brattstrom 2010(77)	Sweden	Karolinska University Hospital	2007-2008	Age ≥ 15 ICU stay > 24 hrs	Unspecified Mechanism	Median 40 (26, 58)	82%	Median 24 (17, 33)	SOFA≥3	164	66	40.24%	3	5
Calvete 2008(78)	Brazil	Hospital Universitário São Vicente de Paulo	Not specified	Hemodynamic instability admitted to ICU Venous catheters inserted	Unspecified Mechanism	35	90	-	SOFA≥3	40	22	55.00%	3	4
Kobbe 2012(79)	Germany	University Hospital Aachen (TR-DGU)	2002-2005	Age ≥ 16 Femoral Shaft Fracture	Unspecified Mechanism	35 (16)	75%	26 (15)	SOFA≥3	616	97	15.75%	3	4
Lefering 2011(80)	Germany & UK	TR-DGU and TARN Database Studies	2000-2010	Trauma Registry	Unspecified Mechanism	-	-	-	SOFA≥3	83051	16669	20.07%	3	5
Lichte 2014(81)	Germany	University Hospital Aachen (TR-DGU)	1993-2008	Age ≥ 16 Tibial Shaft Fracture	Unspecified Mechanism	42 (19)	75%	26	SOFA≥3	2074	535	25.80%	3	5
Lichte 2015(82)	Germany	University Hospital Aachen (TR-DGU)	2005-2012	Trauma Registry	Unspecified Mechanism	-	73%	-	SOFA≥3	40846	10810	26.47%	3	4
Maegele 2007(83)	Germany	TR-DGU Database Study	Not specified	Polytrauma	Unspecified Mechanism	39 (19)	73%	24 (16)	SOFA≥3	8724	1555	17.82%	3	4
Muller	Netherla	Academic Medical	2008-2013	Age ≥ 18	Unspecified	Media	78%	Median	SOFA≥3	930	381	40.97%	3	5

Study ID	Country	Institution (Database)	Data Collection Period	Inclusion Criteria	Study Population	Mean Age (SD)	Males (%)	Mean ISS (SD)	MOF Definition	# Trauma Patients	# MOF Patients	Incidence	OCEBM	MMAT Score
2014(84)	nds, Norway, UK	Center, Netherlands; John Radcliffe Hospital, UK; Oslo University Hospital, Norway; Queen Mary University of London (TARN), UK			Mechanism	n 38 (25, 53)		13 (6, 25)						
Peiniger 2011(85)	Germany	Cologne-Merheim Medical Center (TR-DGU)	2002-2008	Age ≥ 16 ISS ≥ 16 Massive Transfusion Protocol (≥ 10 units)	Unspecified Mechanism	42 (16)	72%	42 (15)	SOFA≥3	1250	653	52.24%	3	5
Steinhausen 2014(86)	Germany	TR-DGU	1993-2008	Polytrauma; Bilateral femoral shaft fractures Required ICU or died in ED	Unspecified Mechanism	33	64%	28	SOFA≥3	379	123	32.45%	3	4
Ulvik 2007(87)	Norway	Haukeland University Hospital	1998-2003	Age > 18	Unspecified Mechanism	-	83%	-	SOFA≥3	322	150	46.58%	3	4
Vogel 2014(88)	USA	Denver Health Medical Center (IHRI)	2005-2008	Age ≥ 18 ED observation unit for ≥ 12 hrs	Unspecified Mechanism	37	72%	9	SOFA≥3	4355	216	4.96%	3	5
Weber 2016(89)	Germany	University Hospital Aachen (TR-DGU)	2002-2010	Age ≥ 16 Femur Fracture	Unspecified Mechanism	-	72%	-	SOFA≥3	5761	1452	25.20%	3	4
Hayakawa 2011(90)	Japan	Hokkaido University Hospital	Not specified	Blunt trauma AIS ≥ 3	Blunt Mechanism	43 (19)	64%	23 (11)	SOFA≥4	45	24	53.33%	3	5
Cabrera 2017(91)	UK	Royal London Hospital (TARN)	2008-2012	Blunt trauma ISS ≥ 25	Blunt Mechanism	Median 36 (26, 53)	75%	Median 33 (27, 39)	SOFA≥5	36	16	44.44%	3	5
Shepherd 2017(92)	UK	Queen Mary University of London, UK (TARN)	2010-2015	Age ≥ 16 Local criteria for full trauma team activation	Unspecified Mechanism	-	80%	-	SOFA≥5	595	469	78.82%	3	5

Study ID	Country	Institution (Database)	Data Collection Period	Inclusion Criteria	Study Population	Mean Age (SD)	Males (%)	Mean ISS (SD)	MOF Definition	# Trauma Patients	# MOF Patients	Incidence	OCEBM	MMAT Score
Frohlich 2013(93)	Germany	Cologne-Merheim Medical Center (TR-DGU)	2002-2011	ISS ≥ 16	Unspecified Mechanism	45	73%	28	SOFA≥6	31154	10201	32.74%	3	4
Halldorsdottir 2018(94)	Sweden	Karolinska University Hospital	2007-2015	Age ≥ 18 ICU Stay > 48 hrs	Unspecified trauma	Median 47 (29, 66)	77	Median 33 (22, 43)	SOFA≥6	97	56	57.73%	3	4
Hazeldine 2017(95)	UK	Queen Elizabeth Hospital, UK (TARN)	2014-2016	Age ≥ 18 ISS ≥ 8 within 1 hr of injury	Unspecified Mechanism	41 (range 18-90)	84%	24 (range 9-66)	SOFA≥6	89	40	44.94%	3	4
Heuer 2009(96)	Germany	University Hospital Essen (TR-DGU)	1993-2005	ISS ≥ 16	Unspecified Mechanism	40 (20)	73%	32 (12)	SOFA≥6	8941	1994	22.30%	3	5
Hilbert-Carius 2018(97)	Germany	TR-DGU	2002-2015	Age ≥ 16 ISS ≥ 9	Unspecified trauma	49 (21)	72	23 (12)	SOFA≥6	36330	10026	27.60%	3	5
Hofman 2020(98)	Germany	University Hospital Aachen (TR-DGU	2010-2015	Age ≥ 18 NISS ≥ 16	Unspecified trauma	51 (21)	72	-	SOFA≥6	467	82	17.56%	3	5
Hussmann 2011(99)	Germany	University Hospital Essen (TR-DGU)	1993-2007	Age ≥ 16 Maximum AIS per body region ≤ 3 GCS 5-13 No packed red blood cell transfusion in emergency trauma room	Unspecified Mechanism	39	79	15	SOFA≥6	1200	84	7.00%	3	3
Innerhofer 2017(100)	Austria	University of Innsbruck	2012-2016	Age 18-80 ISS > 15	Unspecified Mechanism	-	74%	-	SOFA≥6	94	54	57.45%	1	5
Kong 2018(101)	South Korea	Yonsei University Health System	2011-2017	Age > 18	Unspecified trauma	50 (19)	72	28 (11)	SOFA≥6	348	60	17.24%	3	5
Luo 2021(102)	China	Renmin Hospital of Wuhan University	2016-2017	Blunt trauma Age > 16 Survival > 1 day	Blunt trauma	42 (13)	64	23 (7)	SOFA≥6	210	109	51.90%	3	5
Manson	UK	Royal London	2 year	Local criteria for	Unspecified	-	84%	-	SOFA≥6	407	131	32.19%	3	4

Study ID	Country	Institution (Database)	Data Collection Period	Inclusion Criteria	Study Population	Mean Age (SD)	Males (%)	Mean ISS (SD)	MOF Definition	# Trauma Patients	# MOF Patients	Incidence	OCEBM	MMAT Score
2016(103)		Hospital (TARN)	period, dates not specified	full trauma team activation	Mechanism									
Trentzsch 2012(104)	Germany	University Hospital of Munich (TR-DGU)	2002-2008	ISS ≥ 16 Temperature documented on admission	Unspecified Mechanism	44	73	30	SOFA≥6	5197	1524	29.32%	3	4
Trentzsch 2014(105)	Germany	University Hospital of Munich (TR-DGU)	1993-2006	Blunt trauma ISS ≥ 16 ICU stay ≥ 3 days	Blunt Mechanism	Median 36 (26, 53)	75%	Median 33 (27, 39)	SOFA≥6	10343	2438	23.57%	3	5
Trentzsch 2015(106)	Germany	University Hospital of Munich (TR-DGU)	1993-2006	Age ≥ 18 ISS ≥ 9	Unspecified Mechanism	42	73%	25	SOFA≥6	20288	3953	19.48%	3	4
Vogel 2016(107)	USA	Denver Health Medical Center (IHRI)	2011-2013	Age ≥ 18	Unspecified Mechanism	Median 46	68%	9	SOFA≥6	2072	120	5.79%	3	4
Weber 2019(108)	Germany	University Hospital Aachen (TR-DGU)	2002-2013	Age ≥ 16 ISS ≥ 16 Tibia fracture	Unspecified trauma	46 (19)	-	30 (13)	SOFA≥6	4940	1674	33.89%	3	5

[a], multiple cohorts from one study

#, number of

IHRI, Inflammation and the Host Response to Injury Collaborative Program, established in 1998

TARN, Trauma Audit Research Network, established in 1988

TR-DGU, TraumaRegister Deutsche Gesellschaft für Unfallchirurgie, established in 1993

RETRAUCI, Spanish Registry of Trauma in ICU, established

MMAT, Mixed Methods Appraisal Tool

OCEBM, Oxford Center for Evidence-based Medicine.

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Supplemental Digital Content 2. Summary table of studies included in meta-analysis.

Study ID	Country	Institution (± Database)	Data Collection Period	Inclusion Criteria	Study Population	Mean Age (SD)	Males (%)	Mean ISS (SD)	MOF Definition	# Trauma Patients	# MOF Patients	Incidence	OCEBM	MMAT Score
Dewar 2014 (1)[a]	Australia	John Hunter Hospital	2005-2010	Age > 18 ISS > 15	Unspecified Mechanism	47 (21)	69	30 (11)	Denver> 3	8	0	0.00%	3	5
					Unspecified Mechanism				SOFA>4	8	3	37.50%		
					Blunt Mechanism				Denver> 3	132	21	15.91%		
					Blunt Mechanism				SOFA>4	132	81	61.36%		
Giles 2022(2)	Australia	John Hunter Hospital	2012-2019	Age > 16 ISS > 15	Unspecified trauma	45 (19)	75	Median 25 (20, 34)	Denver> 3	663	75	11.31%	3	5
Haupt 2021(3)	Germany	University Hospital of Munich (TR-DGU)	1 year period, dates not specified	Age > 18 ISS ≥ 16	Unspecified trauma	50	57	Median 41	Denver> 3	28	4	14.29%	3	5
Lumsdaine 2014 (4)	Australia	John Hunter Hospital	2011-2012	Age >16 Pelvic, acetabular, femoral shaft or tibial shaft fractures requiring surgical intervention	Unspecified Mechanism	42	78%	19 (13)	Denver> 3	100	11	11.00%	3	5
Moore 1996 (5)	USA	Denver Health Medical Center (IHRI)	1991-1994	Age > 16 ISS > 15 Survival > 48 hrs ICU admission	Unspecified Mechanism	36 (0.7)	77%	25 (0.4)	Denver> 3	457	70	15.32%	3	5
Peerless 2000 (6)	USA	MetroHealth Medical Center	3 year period, dates not specified	Blunt trauma Age ≥ 18 ISS > 15 Mechanically ventilated	Blunt Mechanism	50 (19)	65.6	31 (11)	Denver> 3	62	10	16.13%	3	5

Study ID	Country	Institution (± Database)	Data Collection Period	Inclusion Criteria	Study Population	Mean Age (SD)	Males (%)	Mean ISS (SD)	MOF Definition	# Trauma Patients	# MOF Patients	Incidence	OCEBM	MMAT Score
Richards 2018 (7)	USA	University of Maryland Medical Center	2010-2014	Blunt trauma Age ≥ 18 ISS > 15 Head AIS < 3 ICU admission	Blunt Mechanism	45 (18)	60.7	Median 27 (21, 34)	Denver> 3	507	46	9.07%	3	4
Sauaia 2014 (8)	USA	IHRI Database Study	2003-2010	Blunt trauma Torso Age 16-90 ED arrival < 6 hrs postinjury Blood product transfusion within 12 hrs of ED arrival	Blunt Mechanism	27	65-68	29-34	Denver> 3	1643	223	13.57%	3	4
van Wessem 2018 (9)	Netherlands	University Medical Center Utrecht	2013-2016	ICU Admission	Unspecified Mechanism	Median 45	75%	Median 29	Denver> 3	157	31	19.75%	3	4
Law 1994 (10)	USA	UCLA Medical Center, USA	1991-1992	Age ≥ 18	Unspecified Mechanism	45	85%	38	Denver> 8	13	6	46.15%	3	4
Smail 1995 (11)	France	Bicêtre Hospital	1989-1991	trauma patients requiring ICU care	Unspecified Mechanism	39 (18)	76%	33 (14)	Denver> 8	163	27	16.56%	3	4
Svoboda 1994 (12)	Czech Republic	The Research Institute for Traumatology and Special Surgery, Czechoslovakia	1992	ISS ≥ 16	Unspecified Mechanism	47 (21)	55%	29	Denver> 8	42	14	33.33%	3	5
Nast-Kolb 2001 (13)	Germany	Universitätsklinikum Essen	1975-1990	ISS ≥ 16	Blunt Mechanism	33-40	68-80	28-31	Goris≥4	1361	187	13.74%	3	4
Lingnau 1997 (14)	Austria	University of Innsbruck	1989-1994	Age > 18 ISS ≥ 16 NO antibiotic pretreatment/infection history ICU admission	Unspecified Mechanism	38	78%	35	Goris≥5	310	174	56.13%	1	5
Oberholzer 2000	Switzerland	University Hospital Zurich	1991-1996	Age > 16 ISS ≥ 9	Unspecified Mechanism	41 (2)	71.39	19 (8)	Goris≥5	1276	102	7.99%	3	5

Study ID	Country	Institution (± Database)	Data Collection Period	Inclusion Criteria	Study Population	Mean Age (SD)	Males (%)	Mean ISS (SD)	MOF Definition	# Trauma Patients	# MOF Patients	Incidence	OCEBM	MMAT Score
(15)				Admission < 4 hrs from Injury Survival > 3 days										
Kasotakis 2019(16)	USA	IHRI Database Study	Not specified	Blunt trauma Age > 18 and < 90 ED arrival within 6 hrs of injury	Blunt trauma	44 (20)	66	33 (13)	Marshall >5	488	158	32.38%	3	5
Peralta 2015 (17)	Qatar	Hamad General Hospital	2010-2012	Massive Transfusion Protocol (≥ 10 units) during first 24 hrs postinjury	Unspecified Mechanism	34 (1)	91%	Median 29 (8, 75)	Marshall >5	77	55	71.43%	3	3
Scannell 2010 (18)	USA	Carolinas Medical Center	2001-2007	Blunt trauma ISS ≥ 17 Femoral shaft fracture treated with intramedullary nail	Blunt Mechanism	31 (15)	66%	26 (8)	Marshall >5	205	53	25.85%	3	4
Zolin 2015 (19)	USA	University of Pittsburgh Medical Center	2011-2012	Blunt trauma Age ≥ 17 ICU admission Admission within 6 hrs of injury	Blunt Mechanism	50 (18)	69	Median 16 (10, 21)	Marshall >5	288	39	13.54%	3	4
Wang 2014 (20)	China	Chongqing Medical University	2011-2012	Blunt trauma AIS Chest ≥ 3 Admission within 24 hrs of injury Survival > 7 days	Blunt Mechanism	4 (13)	72%	17 (6)	Marshall >6	57	5	8.77%	3	5
Barea-Mendoza	Spain	RETRAUCI Database Study	2015-2019	Age > 18	Unspecified trauma	50 (19)	78	20 (12)	SOFA>3	9598	965	10.05%	3	5

Study ID	Country	Institution (± Database)	Data Collection Period	Inclusion Criteria	Study Population	Mean Age (SD)	Males (%)	Mean ISS (SD)	MOF Definition	# Trauma Patients	# MOF Patients	Incidence	OCEBM	MMAT Score
2021(21)														
Brattstrom 2010 (22)	Sweden	Karolinska University Hospital	2007-2008	Age ≥ 15 ICU stay > 24 hrs	Unspecified Mechanism	Median 40 (26, 58)	82%	Median 24 (17, 33)	SOFA>3	164	66	40.24%	3	5
Calvete 2008 (23)	Brazil	Hospital Universitário São Vicente de Paulo	Not specified	Hemodynamic instability admitted to ICU Venous catheters inserted	Unspecified Mechanism	35	90	-	SOFA>3	40	22	55.00%	3	4
Lefering 2012 (24)	Germany & UK	TR-DGU and TARN Database Studies	2000-2010	Trauma Registry	Unspecified Mechanism	-	-	-	SOFA>3	83051	16669	20.07%	3	5
Ulvik 2007 (25)	Norway	Haukeland University Hospital	1998-2003	Age > 18	Unspecified Mechanism	-	83%	-	SOFA>3	322	150	46.58%	3	4
Hayakawa 2011 (26)	Japan	Hokkaido University Hospital	Not specified	Blunt trauma AIS ≥ 3	Blunt Mechanism	43 (19)	64%	23 (11)	SOFA>4	45	24	53.33%	3	5
Hazeldine 2017 (27)	UK	Queen Elizabeth Hospital, UK (TARN)	2014-2016	Age ≥ 18 ISS ≥ 8 within 1 hr of injury	Unspecified Mechanism	41 (range 18-90)	84%	24 (range 9-66)	SOFA>6	89	40	44.94%	3	4
Innerhofer 2017 (28)	Austria	University of Innsbruck	2012-2016	Age 18-80 ISS > 15	Unspecified Mechanism	-	74%	-	SOFA>6	94	54	57.45%	1	5
Kong 2018(29)	South Korea	Yonsei University Health System	2011-2017	Age > 18	Unspecified trauma	50 (19)	72	28 (11)	SOFA>6	348	60	17.24%	3	5
Luo 2021(30)	China	Renmin Hospital of Wuhan University	2016-2017	Blunt trauma Age > 16 Survival > 1 day	Blunt trauma	42 (13)	64	23 (7)	SOFA>6	210	109	51.90%	3	5

[a], multiple cohorts from one study

#, number of

IHRI, Inflammation and the Host Response to Injury Collaborative Program, established in 1998

TARN, Trauma Audit Research Network, established in 1988

TR-DGU, TraumaRegister Deutsche Gesellschaft für Unfallchirurgie, established in 1993

RETRAUCI, Spanish Registry of Trauma in ICU

OCEBM, Oxford Center for Evidence-based Medicine

MMAT, Mixed Methods Appraisal Tool

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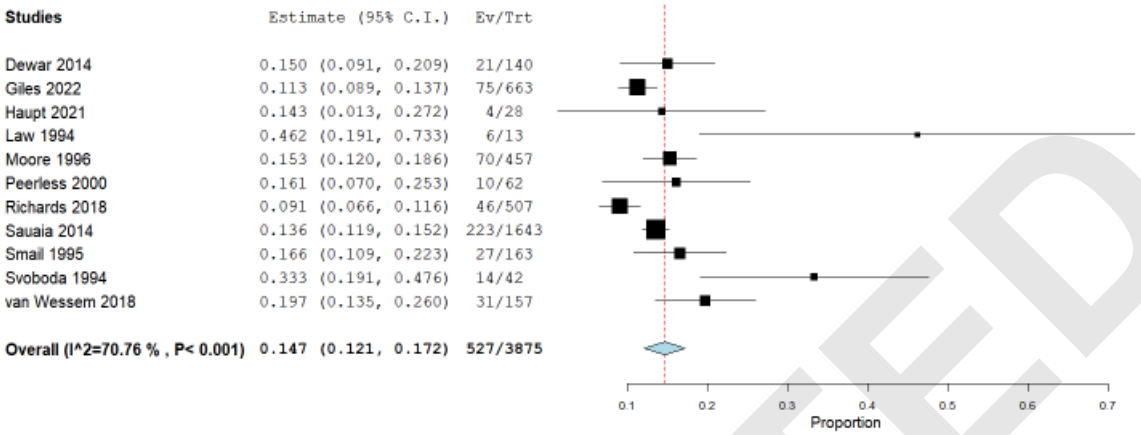
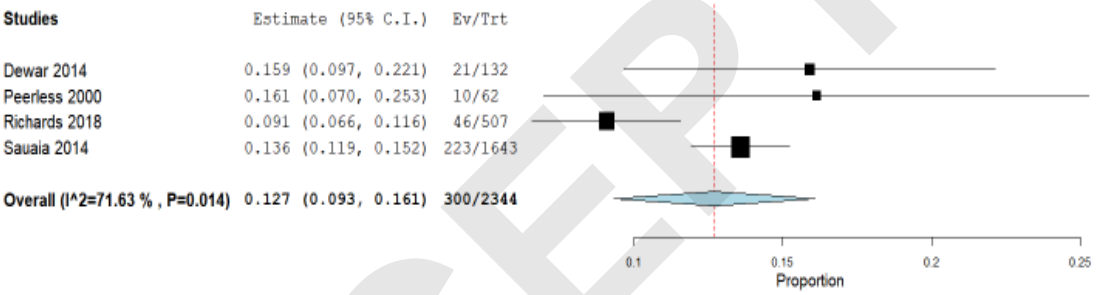
Supplemental Digital Content 3. Forest plots of comparison for MOF incidence based on cut-off values and study populations, where applicable.

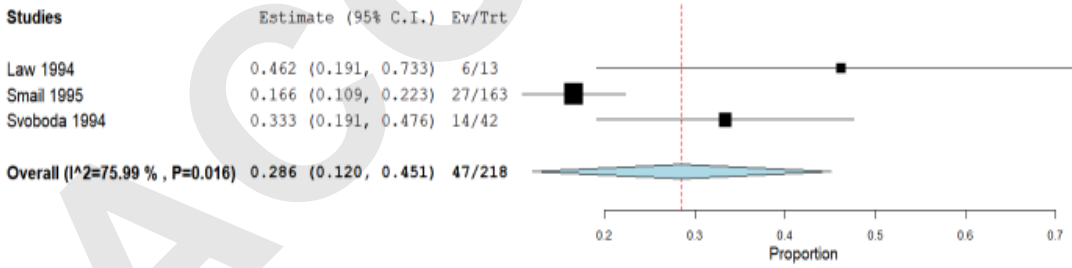
Denver >3



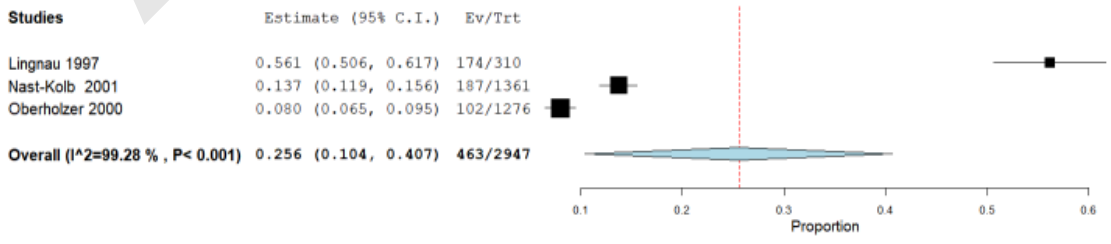
Denver >3, Blunt injuries only



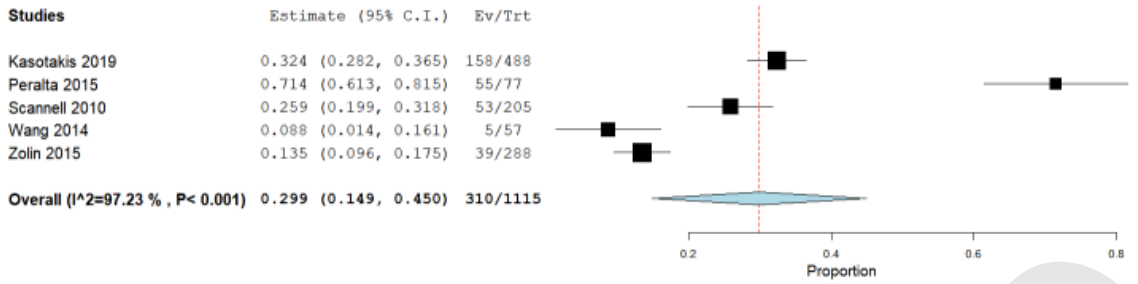
Denver >8



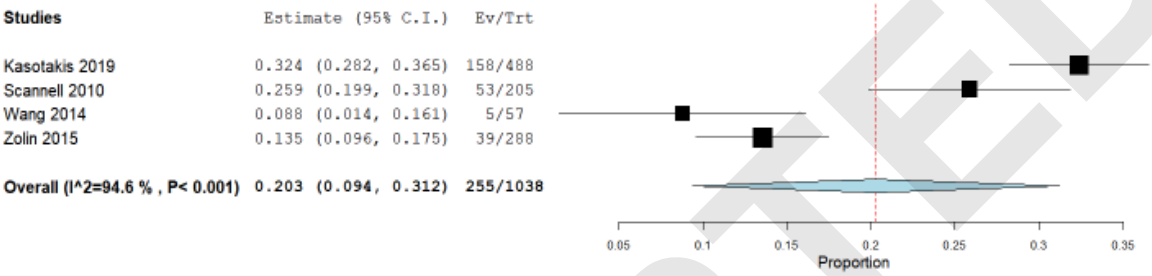
Goris ≥4



Marshall >5



Marshall >5, Blunt injuries only



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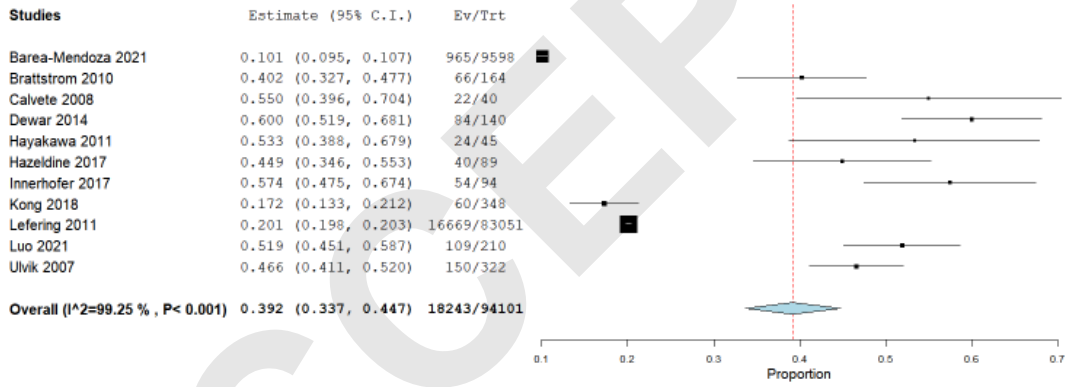

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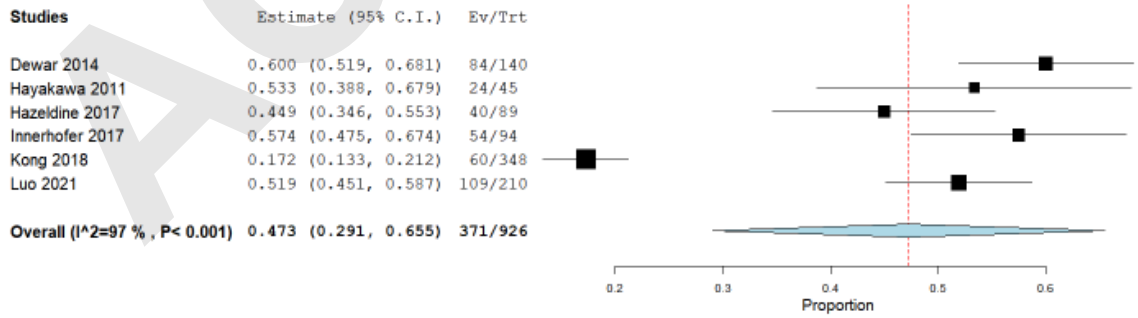

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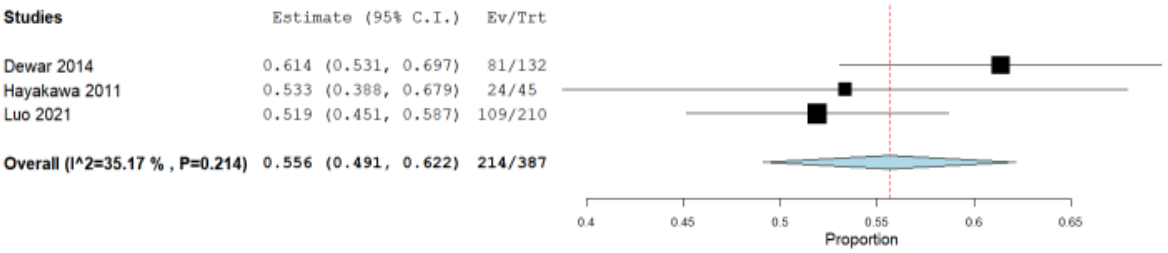
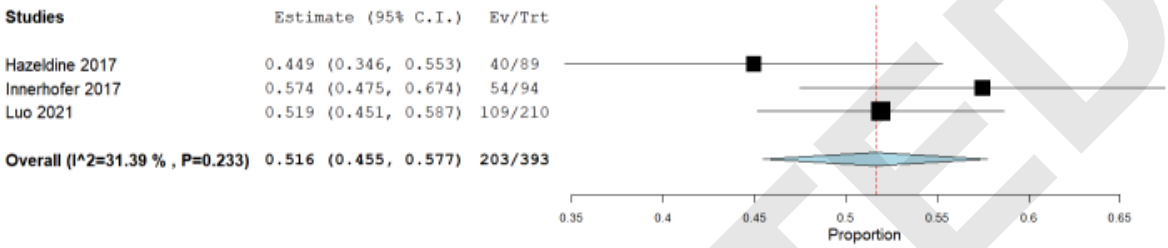


SOFA >6



Incidence of Multiple Organ Failure in Adult Polytrauma Patients

A Systematic Review and Meta-Analysis

Included 353,718 Trauma Patients from 115 Cohorts, from 108 Studies published between 1992-2022

MOF is #1 cause of late death in trauma patients since it was first described 50 years ago.

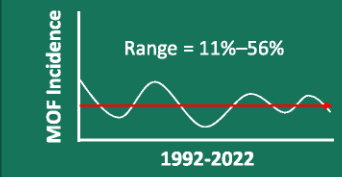
$$\text{Incidence} = \frac{\text{Definition}}{\text{Study Population}}$$

- 40 Different **MOF Definitions**
- 11 Unique **Inclusion Criteria**

Major Findings

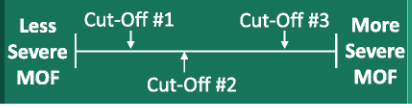
- No Change in **Incidence**
- No Uniform **MOF Definition**
- No Uniform **Study Population**

Incidence is Unchanged in 30 Years



Incidence by MOF Definition

- Many scoring systems
- Multiple cut-offs within scoring systems



Discussion

Unexpectedly, the weighted incidence of MOF was higher in studies using higher cut-off score for definition of MOF, which suggests that study populations were inconsistently defined.

Conclusion

Urgent international consensus on the **definition of MOF** and the **study population at-risk** would finally allow the global trauma community to track its incidence and improve strategies for MOF prevention and management.

Ting R et al. *Journal of Trauma and Acute Care Surgery*.
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