SYSTEMATIC REVIEW

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Composite Primary Outcomes Reported in Studies of Critical Care: A Scoping Review

Prashanti Marella, MD[1,2]
Sansuka De Silva,[3]
Antony G. Attokaran,[4,5]
Kevin B. Laupland, PhD[6,7]
Lars Eriksson, BA[8]
Mahesh Ramanan, MMed[1,7,9]

OBJECTIVE: Composite primary outcomes (CPO) (incorporating both mortality and non-mortality outcomes) offer several advantages over mortality as an outcome for critical care research. Our objective was to explore and map the literature to report on CPO evaluated in critical care research.

DATA SOURCES: PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature, Scopus, and Cochrane Library from January 2000 to January 2024.

STUDY SELECTION: All studies (both non-randomized controlled trial [RCT] and RCT) conducted in ICUs treating adult patients (18 yr old or older) that described CPOs and their definitions, were included for mapping, reporting, and analyzing CPOs without any restrictions.

DATA EXTRACTION: Independent double-screening of abstracts/full texts and data extraction was performed using a pilot-tested extraction template. The data collected included characteristics of CPO, definitions, trends, and death handling techniques used while reporting the CPO.

DATA SYNTHESIS: Seventeen CPOs were extracted from 71 studies, predominantly reported in the setting of pharmaceutical studies (48/71, 67.6%), used RCT methodology (60/71, 84.5%), and were mostly single-center studies (55/71, 77.5%). Ventilator-free days were the most commonly reported CPO (29/71, 40.8%) with marked variability in the definition used and death handling (0 d in 33 studies and −1 d in 7 studies). The most common statistical paradigm used was frequentist (63/71, 88.7%) and the study follow-up time was 90 days with 28 studies using this timeline (28/71, 39.4%). Narrative synthesis highlighted the variability in defining CPO.

CONCLUSIONS: CPOs are an emerging set of outcomes increasingly reported in critical care research. There was significant heterogeneity in definitions used, follow-up times, and reporting trends.

KEYWORDS: composite outcomes; critical illness; intensive care unit; non-mortality; primary outcomes; survival; survivors

The choice of outcome measured (the outcome variables or endpoints) in a clinical trial/study is an important design consideration. The primary outcome is of particular importance because it is the primary determinant that reports on the efficacy of the tested intervention (1). Mortality is an important patient-centered outcome that has been commonly used in critical care research (2). However, its use is declining in critical care trials (3–5). The use of mortality as a primary outcome imposes several limitations including potentially missing an important efficacy signal for reduced morbidity, the need for large sample sizes to detect differences in treatment groups where a direct relation to survival may not be evident, and where there are many potential causes of death that may not be attributable to the intervention (6). Also, with mortality-only outcomes there is no consideration for quality of

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KEY POINTS

Question: What is the range of composite primary outcomes (CPOs) explored in critical care literature?

Findings: This scoping review reported 17 different CPOs in 71 studies which were mostly randomized controlled trials in the setting of pharmaceutical studies. Ventilator-free days were the most commonly reported CPO.

Meaning: CPOs are an emerging set of outcomes increasingly reported in critical care research in recent times. This highlights the need to standardize the definitions and characteristics of CPO to evaluate them further in future critical care trials.

life, for patients' perceptions of their health outcomes, nor is there consideration for patient prioritization of outcomes that matter to them. In other words, using mortality alone is not a meaningful, holistic, patient-centered outcome (7–9).

In the last 3 decades, the use of composite primary outcomes (CPO), often continuous measures, as the primary endpoint has increased in critical care randomized controlled trials (RCTs), possibly due to the increased power and precision, and reduced sample size requirements, when using CPO compared with mortality (10, 11). A composite outcome measure combines two or more distinct endpoints called component endpoints into a single outcome (12–14). Some trials have examined treatments that affected mortality and major morbidity and often adopted a CPO that includes mortality along with other non-fatality endpoints (1, 15). Some CPOs reported in critical care trials include days alive and out of hospital, ventilator-free days, and failure-free days (16, 17). These outcomes incorporate mortality and offer a limited evaluation of morbidity and treatment-associated complications into a composite outcome. Most of these studies measured such outcomes as secondary with short follow-up time and as a part of RCT, which have stringent recruitment criteria and may exclude a wide range of critically ill patients, thus raising questions about their applicability in "real-life scenarios."

This scoping review aimed to investigate the range of CPOs reported in critical care literature. The primary objectives of this review were to: 1) explore and characterize all CPOs reported in the critical care literature, 2) identify their features, and 3) all the definitions and the variability in their use. The secondary objectives were to: 1) investigate the death handling techniques, 2) trends over time 3) summarize the reporting of CPO, and 4) identify gaps in the literature, and define a range of meaningful patient-centered outcomes for future critical care research.

MATERIALS AND METHODS

The protocol was prepublished on open-science framework (18). It was conducted as per the Joanna and Briggs Institute methodology for scoping reviews (19) and reported as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses—extension for scoping reviews (PRISMA-ScR) (20). The composite outcome for the purpose of this scoping review was a combination of mortality and non-lethal outcomes.

Review Questions

The key questions for this scoping review were:

1. What were the CPOs that incorporated mortality along with days alive and free of organ support/ hospital/ICU visitations reported in critical care RCTs?
2. What was the methodology used to derive these outcomes such as chart review, telephonic follow-up, administrative data, or assumption-based?
3. What time frames and study interventions have these outcomes been reported (months/years, pharmaceutical trials vs. non-pharmaceutical studies, etc.)?
4. Is there any variability in definitions used for these outcomes, for example, how were outcomes such as dialysis-free days, and ventilation-free days defined?
5. What were the trends in the use of CPOs and how have they evolved over time?

Study Inclusion and Exclusion Criteria

Both inclusion and exclusion criteria were predefined. All studies (both non-RCT and RCT) conducted in ICU treating adult patients (18 yr old or older) that described CPOs and the definitions used published between January 1, 2000, and January 31, 2024, were included for mapping, reporting, and analyzing CPOs. There were no limitations of language, data collection methods, full articles, or protocols/statistical plans. The exclusion criteria for this scoping review were all the

studies that reported singular primary outcomes (i.e., mortality, ICU length of stay), quality of life outcomes (i.e., reporting outcomes using quality of life scales, patient-reported outcomes), functional outcomes (i.e., frailty, return to work) and reviews/case summaries (systematic review and meta-analyses, rapid reviews, systematized case reviews). The secondary analyses of the primary RCT were included, analyzed, and reported as a single RCT.

Search Strategy and Screening

The search strategy was provided by the academic librarian (**eAppendix 1**, http://links.lww.com/CCX/B445) using which the electronic search of PubMed, Scopus, Embase, Cumulative Index to Nursing and Allied Health Literature, and Cochrane Library was performed. All the results were exported into Endnote V21 and uploaded onto Covidence (Veritas Health Innovation, Melbourne, VIC, Australia) following which two independent reviewers (P.M., S.D.) screened the title and abstracts, included for full-text reviews. The studies that did not fit the inclusion criteria on title and abstract screening were excluded. Full articles were retrieved for review if the title and abstract review were inconclusive and excluded following the review as per protocol. The reasons for the exclusion of studies as categorized on the Covidence included wrong setting, wrong outcomes, wrong study design, wrong study population, and others. All disagreements with study inclusions were resolved by an independent third reviewer (A.A.). All the full texts were retrieved and reviewed by two independent reviewers (P.M., S.D.) for data extraction with disagreements resolved by a third (M.R.). The search was conducted between February 25, 2024, and March 20, 2024, with the last search update on March 26, 2024.

Outcome Data Extraction, Charting, and Reporting

The data were extracted using a standardized form (**eTable 1**, http://links.lww.com/CCX/B445) which was reviewed and approved by all the authors. The data extraction template included the Covidence ID, composite primary outcome, journal report, year of reporting, methodologies, definitions, sites, and statistical analyses. Studies were categorized into pharmaceutical (drug trials) and non-pharmaceutical (evaluating management and intervention/process of care strategies) for data extraction and reporting. All the CPO definitions used in these studies were transcribed verbatim from the reference study on the data extraction template.

The full extraction template is available in eTable 1 (http://links.lww.com/CCX/B445). The data were analyzed and reported using descriptive statistics. We made no contact with the study authors in case of missing data (e.g., missing data handling in studies) and have grouped and analyzed them under not-reported category.

RESULTS

General Characteristics of the Studies

The search strategy used identified 8100 references, of which 147 studies were eligible for further screening and 71 studies that fulfilled all inclusion criteria were retrieved for full-text review and data extraction as shown in the PRISMA-ScR flow chart (**Fig. 1**; and eTables 1 and **5**, http://links.lww.com/CCX/B445). Twenty-five indexed medical journals published literature on CPO in critical illness over the study period, with the largest number (14/71, 20%) being published in the *Journal of American Medical Association* (**Table 1**). Most were conducted in single centers (55/71, 77.5%), predominantly the North American continent, as compared with multi-centers (≥ 2 centers) (16/71, 22.5%) over the study period. The CPO was investigated predominantly in RCT (60/71, 84.5%) and mostly in the setting of pharmaceutical studies (48/71, 67.6%). Other study designs used to report CPO were retrospective cohort studies (7/71, 9.9%), prospective cohort studies (3/71, 4.2%), and before-after studies (1/71, 1.4%). The statistical analyses performed to evaluate the CPO were predominantly frequentist (63/71, 88.7%); however, there was an increasing trend to employ Bayesian analyses (8/71, 11.3%) toward the end of this study period (Table 1). There were 12 studies that proposed to evaluate CPO with protocol and statistical plan only that were included in the review (12/71, 16.9%) (**eTable 3**, http://links.lww.com/CCX/B445).

Characteristics of CPO Reported

A total of 71 studies included in the review reported 17 CPOs. The most commonly reported CPO was

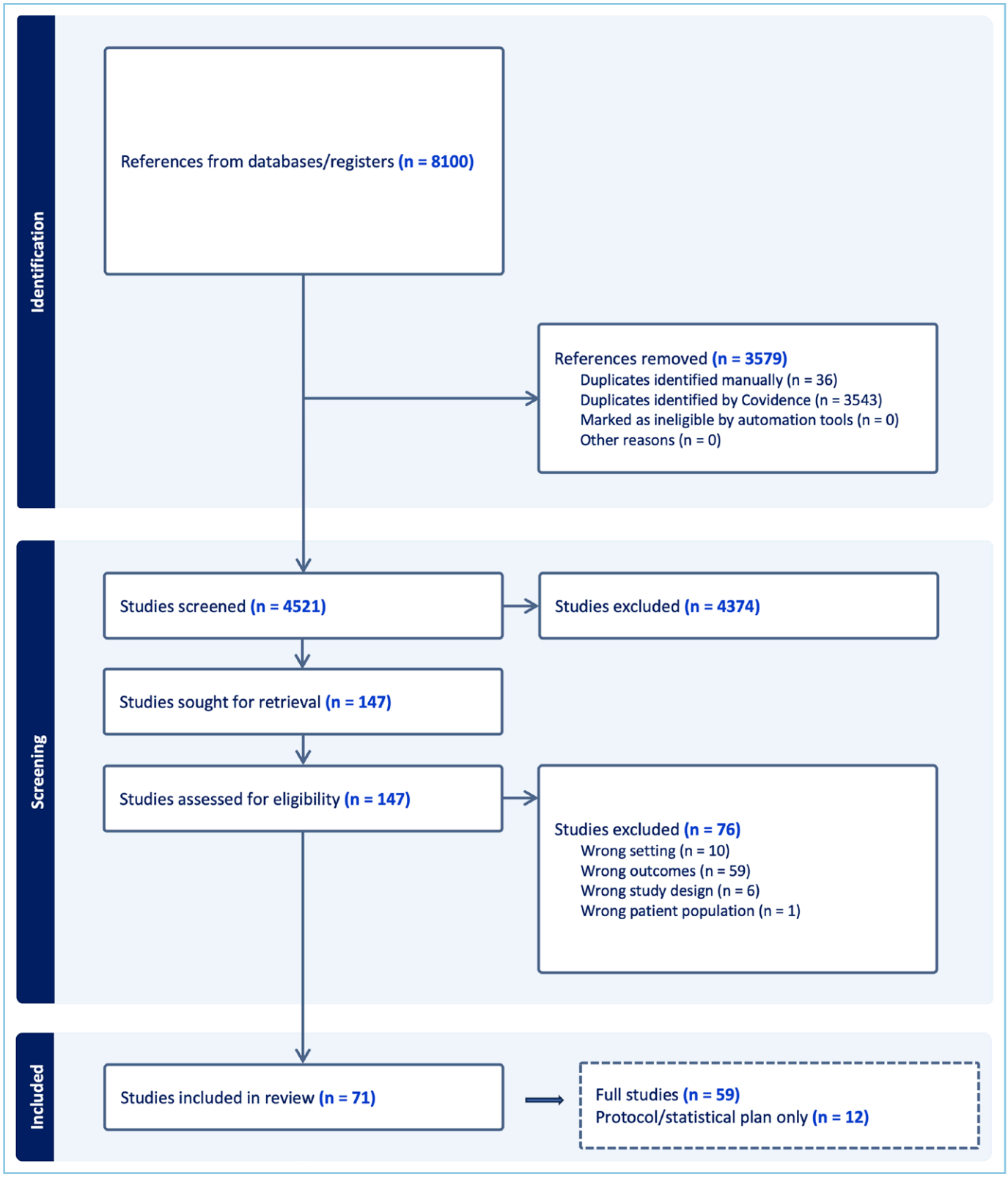

Figure 1. Systematic Reviews and Meta-Analyses—extension for scoping reviews flowchart.

ventilator-free days (29/71, 40.8%) followed by organ support-free days (10/71, 14.1%) (**Table 2**). Ventilator-free days were mostly reported in the setting of pharmaceutical studies (23/48, 47.9%), followed by non-pharmaceutical studies (6/23, 26.1%) (**Table 3**). The death handling (i.e., how death was scored when it

TABLE 1.
General Characteristics of the Studies Included Stratified by Year of Publication

Variable	2000–2010 (*n* = 5)	2011–2020 (*n* = 35)	2021–2024 (*n* = 31)	Total (*n* = 71)
Journal, *n* (%)				
JAMA	2 (40)	9 (25.7)	3 (9.7)	14 (19.7)
Trials	0 (0)	6 (17.1)	6 (19.4)	12 (16.9)
NEJM	0 (0)	3 (8.6)	2 (6.5)	5 (7.1)
Acta Anaethesiol Scand	0 (0)	0 (0)	4 (12.9)	3 (4.2)
Crit Care	1 (20)	1 (2.9)	2 (6.9)	4 (5.6)
Crit Care Med	1 (20)	2 (5.7)	0 (0)	3 (4.2)
Thorax	0 (0)	0 (0)	1 (3.2)	1 (1.4)
Int J Antimicrob Agents	0 (0)	1 (2.9)	0 (0)	1 (1.4)
ICM	0 (0)	2 (5.7)	2 (6.9)	4 (5.6)
Anaesth Intensive Care	0 (0)	1 (2.9)	0 (0)	1 (1.4)
PLoS One	0 (0)	1 (2.9)	0 (0)	1 (1.4)
BMJ Open	0 (0)	1 (2.9)	0 (0)	1 (1.4)
JAMA Intern Med	0 (0)	1 (2.9)	0 (0)	1 (1.4)
Heart Lung	0 (0)	0 (0)	1 (3.2)	1 (1.4)
JAMA Surgery	0 (0)	0 (0)	1 (3.2)	1 (1.4)
J Crit Care	0 (0)	1 (2.9)	1 (3.2)	2 (2.8)
Infect Dis	0 (0)	0 (0)	1 (3.2)	1 (1.4)
Int J Radiat Oncolog Biol Phys	0 (0)	0 (0)	1 (3.2)	1 (1.4)
Crit Care Resus	0 (0)	1 (2.9)	0 (0)	1 (1.4)
Am J Resp Crit Care Med	1 (20)	0 (0)	2 (6.9)	3 (4.2)
J Clin Anaesth	0 (0)	1 (2.9)	0 (0)	1 (1.4)
Resuscitation	0 (0)	0 (0)	1 (3.2)	1 (1.4)
Kidney Med	0 (0)	0 (0)	1 (3.2)	1 (1.4)
J Intensive Care Med	0 (0)	1 (2.9)	1 (3.2)	2 (2.8)
LANCET Resp Med	0 (0)	3 (8.6)	1 (3.2)	4 (5.6)
Study sites, *n* (%)				
Multi-center[a] (≥ 2 countries)	0 (0)	6 (17.1)	10 (32.2)	16 (22.5)
Single-center[b]	5 (100)	29 (82.9)	21 (67.7)	55 (77.5)
Sample size, *n* (average)	579 (115.8)	1,17,769 (3,463.79)	96,851 (3,026.59)	2,15,199
Study design, *n* (%)				
1. RCT[c]	5 (100)	27 (77.1)	28 (90.3)	60 (84.5)
2. Retrospective cohort	0 (0)	5 (14.3)	2 (6.5)	7 (9.9)
3. Before-after study	0 (0)	1 (2.9)	0 (0)	1 (1.4)
4. Prospective cohort	0 (0)	2 (5.7)	1 (3.2)	3 (4.2)
Study intervention, *n* (%)				
1. Pharmaceutical[d]	5 (100)	25 (71.4)	18 (58.1)	48 (67.6)
2. Non-pharmaceutical[e]	0 (0)	12 (34.2)	11 (35.5)	23 (22.4)

(*Continued*)

TABLE 1. (*Continued*)
General Characteristics of the Studies Included Stratified by Year of Publication

Variable	2000–2010 (*n* = 5)	2011–2020 (*n* = 35)	2021–2024 (*n* = 31)	Total (*n* = 71)
Protocols only (**eTable 2**, http://links.lww.com/CCX/B445 in supplement)	0 (0)	6 (17.1)	6 (19.4)	12 (16.9)
Statistical methods, *n* (%)				
1. Frequentist	5 (100)	33 (94.3)	25 (80.6)	63 (88.7)
2. Bayesian	0 (0)	2 (5.7)	6 (19.3)	8 (11.3)

JAMA = Journal of American Medical Association, NEJM = New England Journal of Medicine, BMJ = British Medical Journal, ICM = Intensive Care Medicine, LANCET = independent, international weekly general medical journal.
[a]Multi-centers: Most of the collaborations were between the United States and European nations, Australia and European nations, and Asia-Pacific.
[b]Single-centers: Australia, Canada, The United States, Brazil, Netherlands, France, Finland, Denmark, The United Kingdom, Italy, Spain.
[c]Randomized controlled trials.
[d]Pharmaceutical intervention- evaluating the efficacy of medication/drug (e.g., haloperidol on delirium) on the study outcome of interest. These could be placebo-controlled or compared with other drugs, or different doses of the same drug.
[e]Non-pharmaceutical interventions studies evaluating the impact of an intervention (e.g., delirium interventions) on the study outcome of interest or studies evaluating the impact of a management strategy (e.g., fluid balance in acute respiratory distress syndrome) on the study outcome of interest.
n refers to number. Categorical variables are reported using numbers and percentages.

occurred during the follow-up period) was reported as 0 days in 33 studies and –1 days in 7 studies, whereas 31 studies did not specify. The most common definition used was presented in the "days alive and free of XX" format. There was a wide range of definitions used to define these 17 outcomes, and different ways of defining the same CPO in various studies have been published in the online supplement (**eTable 4**, http://links.lww.com/CCX/B445).

CPO—Methodological Characteristics of the Studies

CPO—Reporting Characteristics. The data collection methods used to report the CPO in the non-RCT setting mostly involved the use of administrative data (13/71, 18.3%) with predominant reporting in the setting of non-pharmaceutical studies (8/23, 34.8%). The other data collection methods used were chart reviews (3/71, 4.2%) mostly in the setting of pharmaceutical studies (2/43, 4.2%), and phone calls in the setting of non-pharmaceutical studies(1/23, 4.3%). None were assumption-based. The missing data were frequently reported in pharmaceutical studies (34/48, 70.8% versus 7/23, 30.4%). The missing data went unreported in most of the non-pharmaceutical studies (16/23, 69.6%) (**Table 4**).

CPO—Effect Measures

CPOs were predominantly analyzed using frequentist methods (63/71, 88.7%), whereas some studies reported using Bayesian methods (8/71, 11.3%) (Table 1). The median with interquartile range (IQR) (30/71, 42.3%) was the most common effect measure to analyze CPOs, which mostly was in the setting of pharmaceutical studies (19/48, 39.6%). Other effect measures used to report CPO were mean with SD (27/71, 38%), hazards ratio with 95% CIs (6/71, 8.5%), mean difference (3/71, 4.2%), odds ratio with 95% CI (3/71, 4.2%), non-inferiority margin with 95% CI (1/71, 1.4%) and posterior probability (1/71, 1.4%) (Table 4). The most common statistical test used to report the CPO was the Mann-Whitney *U* test (16/71, 22.5%) followed by the Wilcoxon rank sum test (13/71, 18.3%) (**eFig. 1**, http://links.lww.com/CCX/B445). There were no studies that used zero-inflated statistical techniques for analyzing the CPO.

CPO—Study Follow-Up Time and Reporting

The study follow-up times were different from the time points for studying the CPO. The shortest study follow-up time was 14 days (1/71, 1.4%) with the longest being more than 1 years (2/71, 2.8%). The

TABLE 2.
Composite Primary Outcome Characteristics

CPO[a] Reported ($n = 17$)	Frequency of Reporting, n (%), Total Studies = 71	Components of CPO	Death Handling[b] (d)		
			−1 d (n)	0 d (n)	Not Reported (n)
Ventilator-free days	29 (40.8)	Days alive and ventilator-free	2	19	8
Organ support-free days	10 (14.1)	Days alive and free of organ support	4	5	1
Days alive and out of hospital	5 (7.1)	Days alive and discharged from hospital	–	2	3
ICU-free days	5 (7.1)	Days alive and discharged from ICU	–	2	3
Delirium and coma-free days	8 (11.3)	Days alive without delirium and coma	–	2	6
Supplemental oxygen-free days	1 (1.4)	Days alive and free of supplemental oxygen	1	–	–
Days alive and free of renal replacement	3 (4.2)	Days alive and free of CKD and renal replacement	–	–	3
Kidney failure-free days	1 (1.4)	Days alive and free of CKD defined by Acute Kidney Injury Network criteria	–	–	1
Days alive at home	1 (1.4)	Days alive after ICU admission and no hospital admission	–	–	1
Institution-free days	1 (1.4)	Mortality and event-free days.	–	1	–
Antibiotic-free days	1 (1.4)	Days alive and antibiotic-free	–	–	1
Mortality and multi-organ-free days	1 (1.4)	Mortality and Multi-organ failure-free	–	–	1
Days alive with normal arterial lactate, vasopressor/inotrope-free	1 (1.4)	Days alive with normal arterial lactate and free of vasopressor/ inotrope support	–	–	1
All-cause mortality and ventilator-free days	1 (1.4)	Composite of all-cause mortality and ventilator-free days	–	1	–
Event-free survival	1 (1.4)	Alive and free of cardio-respiratory support	–	–	1
Composite outcome of major adverse event	1 (1.4)	Death and major adverse event	–	–	1
ICU and Ventilator-free days	1 (1.4)	Alive and free of ICU admission and ventilation	–	1	–

CKD = Chronic Kidney disease, CPO = composite primary outcome.

[a]The composite primary outcome is a combination of mortality and a non-lethal outcome. The most commonly used definition for a composite primary outcome has been used for reporting. The variability in definitions used to define the composite primary outcomes has been reported in the supplementary material.

[b]Death handling refers to how death has been reported if the patient died before the time point of reference. Some studies used −1 d if the patient dies before the time point whereas others reported 0 d if the patient dies before the timepoint of reference.

Emdashes refer to studies that did not report on death handling.

TABLE 3.
Composite Primary Outcomes Stratified by Study Intervention

	Study Intervention ($n = 71$)	
Composite Primary Outcome ($n = 17$)	**Pharmaceutical ($n = 48$)**	**Non-pharmaceutical ($n = 23$)**
Ventilator-free days	23 (47.9%)	6 (26.1%)
Organ support-free days	8 (16.6)	2 (8.7%)
Days alive and out of hospital	3 (6.3%)	2 (8.7%)
ICU-free days	2 (4.2%)	3 (13%)
Delirium and coma-free days	7 (14.6%)	1 (4.3%)
Supplemental oxygen-free days	1 (2.1%)	0 (0)
Days alive and free of renal replacement	1 (2.1%)	2 (8.7%)
Kidney failure-free days	1 (2.1%)	0 (0%)
Days alive at home	0 (0%)	1 (4.3%)
Institution-free days	0 (0%)	1 (4.3%)
Antibiotic-free days	1 (2.1%)	0 (0%)
Mortality and multi-organ-free days	0 (0%)	1 (4.3%)
Days alive with normal arterial lactate, vasopressor/ inotrope-free	0 (0%)	1 (4.3%)
All-cause mortality and ventilator-free days	0 (0%)	1 (4.3%)
Event-free survival	0 (0%)	1 (4.3%)
Composite outcome of major adverse event	1 (2.1%)	0 (0%)
ICU and ventilator-free days	0 (0%)	1 (4.3%)

Composite primary outcome is represented as *n* (%).

most common study follow-up time was 90 days with 28 studies using this timeline for their study (28/71, 39.4%). Other study follow-up times used for reporting were 21 days (2/71, 2.8%), 28 days (14/71, 19.7%), 30 days (2/71, 2.8%), 60 days (6/71, 8.5%), 180 days (8/71, 11.3%), and 1 years (8/71, 11.3%) (Table 4).

Trends in Reporting CPO

The number of studies using CPOs steadily increased over the 23 years with 5 studies from 2000 to 2010 (5/71, 7%), 35 studies from 2011 to 2020 (35/71, 49.3%), and 31 studies from 2021 to January 2024 (31/71, 43.7%) (Table 1). The highest number of studies reporting CPO was 14 in the year 2021 (**Fig. 2**). There was a rising trend in general across all study types to employ CPO for outcome evaluation across the last 2 decades with both pharmaceutical and non-pharmaceutical studies. There were 28 RCTs conducted between 2021 and January 2024 that have used and reported CPO. There was also a rising trend to use Bayesian statistical analyses, reported in 6 studies between 2021 and 2024 compared with 2 studies before 2021 (Table 1).

DISCUSSION

In this scoping review, we explored, mapped, and analyzed all studies that evaluated 17 CPOs in critical care research over a 2-decade period. We reported on the currently available literature and identified gaps. CPOs were increasingly reported over the study period in both prospective and retrospective study designs in various settings. Ventilator-free days were the most commonly reported CPO with variable definitions and a wide range of follow-up times. There was also increasing use of Bayesian statistical methods alongside conventional statistics to analyze these outcomes.

A composite endpoint consists of two or more single events combined in one outcome that should represent an overall clinically relevant and valid measure of clinical

TABLE 4.
General Characteristics of the Studies Assessed Stratified by Study Intervention

Variable	Study Intervention (*n* = 71)	
	Pharmaceutical (*n* = 48)	Non-pharmaceutical Intervention (*n* = 23)
Data collection methods, *n* (%)		
Chart reviews	2 (4.2)	1 (4.3)
Phone calls	0 (0)	1 (4.3)
Administrative data	5 (10.4)	8 (34.8)
Assumption	0 (0)	0 (0)
Missing data, *n* (%)		
Reported	34 (70.8)	7 (30.4)
Not reported	14 (29.2)	16 (69.6)
Effect measure, *n* (%)		
Mean difference	3 (6.3)	0 (0)
Mean with SD, 95% CI	19 (39.6)	8 (34.8)
Median with interquartile range	19 (39.6)	11 (47.8)
Odds ratio, 95% CI	3 (6.3)	0 (0)
Non-inferiority margin, 95% CI	1 (2.1)	0 (0)
Hazard ratio, 95% CI	2 (4.2)	4 (17.4)
Posterior probability	1 (2.1)	0(0)
Follow-up time frame[a], *n* (%)		
14 d	1 (2.1)	0 (0)
21 d	2 (4.2)	0 (0)
28 d	13 (27.1)	1 (4.3)
30 d	0 (0)	2 (8.7)
60 d	6 (12.5)	0 (0)
90 d	16 (33.3)	12 (52.2)
180 d	6 (12.5)	2 (8.7)
365 d/1 yr	4 (8.3)	4 (17.4)
> 1 yr	0 (0)	2 (8.7)

[a]Studies reported different timelines for assessing the composite primary outcome and the total study duration. The study timeline in the table refers to the total study duration which also included reporting on other outcomes.
n represents number of studies assessed.

benefit due to treatment. It is possible to combine binary or time-to-event endpoints (21). Composite endpoints usually refer to combined morbidity and mortality endpoints. These may also be a combination of objective (e.g., laboratory measurements) and subjective outcomes (e.g., pain); in this case, the clinical relevance of overall results can be more difficult to interpret (22). This scoping review found that most CPOs were reported in the "days alive and without" format. The morbidity markers ranged from being free of ventilation, delirium, organ support-free days, vasopressors, or a discharge from ICU/hospital (23–26). The most commonly reported CPO in this study was ventilator-free days which was defined with significant heterogeneity and studied over a wide range of timeframes (19, 23, 27) and these findings have been supported in a scoping review (17). A systematic review has reported that the changes in the definition of composite outcomes during the trial were common and had been

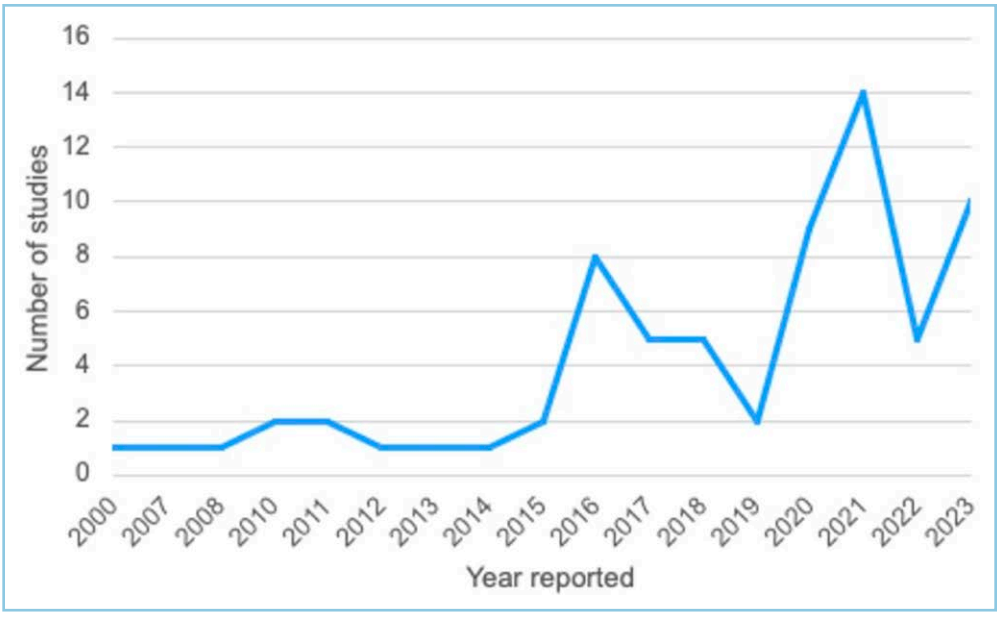

Figure 2. Trends in reporting composite primary outcomes.

a source of biased reporting (28). However, this was not demonstrated in our review.

In general, composite outcomes reported as a singular outcome, evaluate the overall treatment effect (21). The number of components of a composite outcome should be limited to 4 to avoid difficulties in the interpretation of the results (22). In this review, of the 17 CPOs we evaluated, only two CPOs had more than three components- composite outcome of major adverse event (composite of major adverse event at 90 days: all-cause death, myocardial Infarction, new-onset heart failure, re sternotomy, stroke, major arrhythmias, major bleeding, infection, and acute kidney injury) (29) and days alive with normal arterial blood lactate and without vasopressor or inotrope (days alive in 30 days—with normal arterial blood lactate [first confirmed value of < 2 mmol/L] and without any inotropic or vasopressor agent) (30). The evidence does support the use of composite outcomes to be considered if it allows a better representation of the overall benefit of the intervention than a single endpoint (22).

Our group previously evaluated institution-free days (IFDs) as a CPO in a retrospective cohort of critically ill patients, that captured patients' journey from the ICU, across the hospital, and through to the community over 1 year (9). Unlike most other CPOs in critical care, IFD encompassed mortality and any health facility visitations following index discharge that would impact their quality of life. These included readmissions, to either hospital or the emergency department, mental health, rehabilitation (both outpatient and inpatient), dialysis, chemotherapy, and any other outpatient therapy sessions that would necessitate a trip to a healthcare institution. Apart from this study, there has been minimal reporting of composite outcomes that encompassed survival and life thereafter in a holistic manner in critically ill patients (7, 9). This scoping review confirms that this remains a key evidence gap in the reporting of critical care outcomes. It is also noteworthy that health-related quality of life and post-intensive care syndrome as non-mortality outcomes in ICU have been areas of extensive research in recent times (17, 31, 32).

The strengths of this scoping review are first, its adherence to reporting guidelines. Second, the search strategy and syntax were provided by an academic librarian providing thoroughness to the search. Third, a prepublished protocol increases the transparency of the report and avoids potential duplication of the research question. Fourth, there was an independent review of the data collection which enhances the robustness of reporting. There were, however, some limitations to consider. One of these was the inclusion of study protocols, pending completion and reporting. It is not known whether these proposed studies will report as per the published protocols. There is an intrinsic drawback in reporting CPO that they have been limited by the effect size of each of the components and there is a strong recommendation to report each of these outcomes as secondary outcomes to enhance the validity of the study outcome in trials. While being thorough, it is possible that some studies that reported CPOs were missed as they may not be indexed in the databases we searched. We only included studies with a composite outcome as the primary outcome. It

is possible, indeed likely, that many more studies reported secondary outcomes, which were composite outcomes. However, this was a pre-specified inclusion criterion for this review because the aim was to evaluate CPOs which are the most likely to have an impact on the conclusions of studies and subsequently, investigated in clinical practice.

CONCLUSIONS

CPOs have been increasingly reported in the critical care literature with significant heterogeneity in definitions used, reporting time frames, and analytic paradigms. The comparability and generalizability of CPO may be enhanced by standardizing the definitions and other outcome characteristics.

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1 *Department of Intensive Care Medicine, Caboolture Hospital, Caboolture, QLD, Australia.*

2 *School of Medicine, University of Queensland, Brisbane, QLD, Australia.*

3 *Monash University, Melbourne, VIC, Australia.*

4 *Department of Intensive Care Medicine, Rockhampton Hospital, Rockhampton, QLD, Australia.*

5 *University of Queensland, Rural Clinical School, Rockhampton, QLD, Australia.*

6 *Department of Intensive Care Medicine, Royal Brisbane and Womens Hospital, Brisbane, QLD, Australia.*

7 *Queensland University of Technology, Brisbane, QLD, Australia.*

8 *University of Queensland, Brisbane, QLD, Australia.*

9 *Critical Care Division, The George Institute for Global Health, University of New South Wales, Sydney, NSW, Australia.*

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For information regarding this article, E-mail: prashanti.marella@health.qld.gov.au

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