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SYSTEMATIC REVIEW

Assessing the one-month mortality impact of civilian-setting prehospital transfusion: A systematic review and meta-analysis

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Abstract

Background: Based on convincing evidence for outcomes improvement in the military setting, the past decade has seen evaluation of prehospital transfusion (PHT) in the civilian emergency medical services (EMS) setting. Evidence synthesis has been challenging, due to study design variation with respect to both exposure (type of blood product administered) and outcome (endpoint definitions and timing). The goal of the current meta-analysis was to execute an overarching assessment of all civilian-arena randomized controlled trial (RCT) evidence focusing on administration of blood products compared to control of no blood products.

Method: The review structure followed the Cochrane group's Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA). Using the Transfusion Evidence Library (transfusionevidencelibrary.com), the multidatabase (e.g. PubMed, EMBASE) Harvard On-Line Library Information System (HOLLIS), and GoogleScholar, we accessed many databases and gray literature sources. RCTs of PHT in the civilian setting with a comparison group receiving no blood products with 1-month mortality outcomes were identified.

Results: In assessing a single patient-centered endpoint—1-month mortality—we calculated an overall risk ratio (RR) estimate. Analysis of three RCTs yielded a model with acceptable heterogeneity ($I^2 = 48\%$, Q-test $p = 0.13$). Pooled estimate revealed civilian PHT results in a statistically nonsignificant ($p = 0.38$) relative mortality reduction of 13% (RR 0.87, 95% CI 0.63–1.19).

Conclusions: Current evidence does not demonstrate 1-month mortality benefit of civilian-setting PHT. This should give pause to EMS systems considering adoption of civilian-setting PHT programs. Further studies should not only focus on which formulations of blood products might improve outcomes but also focus on which patients are most likely to benefit from any form of civilian-setting PHT.

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INTRODUCTION

In the military trauma setting, prehospital transfusion (PHT) is a firmly evidenced means to reduce preventable death.[1] Increasing awareness of military-setting mortality benefits of PHT—defined in this review as in others[2] to include prehospital administration of whole blood (WB), red blood cells (RBCs), plasma (any form), or other blood product(s)—has spurred PHT adoption in some civilian U.S. jurisdictions[3] and consideration in others. Civilian PHT (CivPHT) has support from national organizations such as the American College of Surgeons and American College of Emergency Physicians (in a joint position statement[4]) as well as favorable mention on U.S. government websites (e.g., https://www.usfa.fema.gov/index.html).

Despite the common sense appeal of a presumption that military-setting PHT evidence can be extrapolated to civilian settings, such a presumption is arguably insufficient basis for widespread promulgation of transfusion programs across nonmilitary emergency medical services (EMS) systems. With regard to CivPHT patient eligibility, components (and ratios), complications (e.g. alloimmunization), and resource requirements, questions remain and debate continues.[2,5,6]

Issues surrounding CivPHT are being actively addressed by ongoing randomized trials such as the Type O Whole Blood and Assessment of Age During Prehospital Resuscitation (TOWAR, clinicaltrials.gov 04684719). The fact that such trials have not yet been completed has not precluded calls for EMS systems planners to consider widespread CivPHT.[7]

We conducted the current systematic review and meta-analysis (MA) to summarize existing randomized controlled trial (RCT) data on mortality effects of CivPHT versus nontransfused controls (i.e., patients receiving no blood products). Our goal was to evaluate and briefly describe all CivPHT RCT evidence addressing a single, clearly important patient-centered outcome: 1-month mortality. We aimed to gather, review, and execute MA on all RCT data evaluating 1-month survival in patients randomized to CivPHT versus patients receiving no prehospital blood products.

METHODS

Review framework and PICO (participants–intervention–comparator–outcome)

Review framework

The review structure followed the Cochrane group's Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA).[8,9] The PRISMA checklist is found in the Supplement. Bias was evaluated using the evidentiary quality rating system Grading of Recommendations Assessment, Development, and Evaluation (GRADE) and risk of bias (RoB2, including the RoB2 version for cluster-randomized trials) as recommended by the Cochrane group.[10,11] Our review aim did not dictate formal GRADE evaluation for different endpoints; we rather applied GRADE principles to the 1-month mortality endpoint.[12]

Participants

Participants were any patients, of any age or diagnosis, receiving CivPHT. The key differentiation for this MA was that included studies assessed civilian-arena patients (rather than those in a military setting).

Interventions

Existing studies describing out-of-hospital transfusion have employed a variety of blood and blood components. To be maximally inclusive of CivPHT studies, we judged it best to include within the term "prehospital transfusion" the institution of prehospital therapy with any blood product (WB, RBC, plasma, cryoprecipitate, fibrinogen, prothrombin complex concentrate). In our broad definition of transfusion, we chose to follow the path set by a recent multidisciplinary consensus-building CivPHT conference.[2]

Comparator

The comparator in the studies we assessed was simply defined as "non-PHT" care. The non-PHT patients in studies could have received crystalloid alone or additional nontransfusion therapies such as tranexamic acid. Since our goal was assessment of CivPHT versus no-transfusion controls, we excluded studies in which there was no nontransfusion comparator; this meant, for example, exclusion of three recent studies[13–15] assessing benefit gained by adding plasma components to RBCs. We did plan to include studies (ultimately, one[16] was included) in which some patients in the "usual care" control group may have received a blood product, but such studies were included only if reporting allowed restriction of our analysis to the subset of cases receiving no prerandomization blood products.

Outcome

To keep our MA simply focused on a single outcome of undoubted patient-centered import, we chose to assess mortality. The time frame of assessment was set a priori to be 1 month (either 4 weeks or 30 days).

Identification of studies to include in review

The study set was constituted through a multistep process. We first executed a literature search (in October 2023) using methods advocated by experts in evidentiary assembly.[17] Recent subject-area

reviews (e.g., van Turenhout et al.,[18] Coccolini et al.,[19] Tucker et al.[20]) were used to facilitate capture of relevant studies.

Details of the literature search are outlined in the Supplement. Using the Transfusion Evidence Library (http://www.transfusionevidencelibrary.com/), the multidatabase (e.g. PubMed, EMBASE) Harvard On-Line Library Information System (HOLLIS), and GoogleScholar, we accessed many databases and gray literature sources. Search terms—"prehospital" with variants (e.g., "ambulance," "out-of-hospital") and "transfusion" with variants including different transfusates (e.g. "plasma")—were broad. Records were all assessed by title or abstract, with records having any question of relevance reviewed as full text.

To avoid repetition of case counting and minimize bias risk, we excluded any post hoc studies[21,22] incorporating cases previously reported in studies already included in the MA. We also excluded modeling studies (e.g., Roberts et al.[23]) and studies that did not report comparison of CivPHT against a nontransfusion control group.

Software

Search records were downloaded from HOLLIS and GoogleScholar for initial review and filtering (e.g., of duplicates). Selected studies were imported into a reference manager (EndNote, clarivate.com).

All statistical analysis was executed using Stata (version 17MP). Stata was also used to generate statistical plots.

Reporting and data analysis

Our MA emphasized risk ratio (RR), reported with 95% confidence interval (CI), as the most intuitive and preferred MA metric for binary outcome data.[24,25] An initial plan to calculate risk difference (absolute risk reduction) proved impractical due to markedly different baseline mortalities in the identified RCTs.

For RR results, directionality was set such that a RR of less than one indicated a lower risk of death. Therefore, in this MA a result of RR <1 would indicate CivPHT reduction in mortality.

Using methodology similar to that in previous CivPHT reviews,[18] we chose a random-effects (RE) model: the (Stata default) restricted maximum likelihood approach. We planned to calculate a prediction interval (to provide a range of likely mortality reduction found in future CivPHT studies), but our ultimately defined study *N* was insufficient to support such calculation.[25] Both clinical and methodological heterogeneity were known concerns. Heterogeneity was evaluated with Q (for presence) and I^2 (for quantification), with I^2 interpretations per Cochrane recommendations.[25]

Elucidation of mechanisms to explore for methodological heterogeneity commenced with funnel and Galbraith plotting to assess for small-study (e.g., publication) bias. Outlier identification incorporated Galbraith plots and leave-one-out analyses. Finally, MA was repeated using fixed-effect modeling, to assess whether estimates differed substantially from RE estimates (since such differences could be an indicator of publication bias).[26] Our ultimate study *N* was insufficient to enable other preplanned analyses (e.g., Egger testing, meta-regression).[25,26]

RESULTS

Identification of studies to be reviewed

After initial search and title/abstract reviews, 44 records were reviewed in full text before the final study set of $N=3$ was assembled (Figure 1 and Table 1). In addition to the important interstudy differences suggested in Table 1 (CivPHT therapy and mortality rate), there were additional sources of potential differences between RCT populations. Table 2 outlines highlights of each studies' markers for acuity, logistics, and crystalloid/blood product therapy. RCTs' reporting differences precluded tabulating identical metrics. Table 2 findings are indicative of potential heterogeneity in study populations (e.g., relatively lesser transfusion and relatively lower mortality in COMBAT vs. RePHILL).

Study findings

This MA focuses on 1-month mortality. Study-level main findings for this endpoint are in Table 3. Sensitivity analyses reported in the three

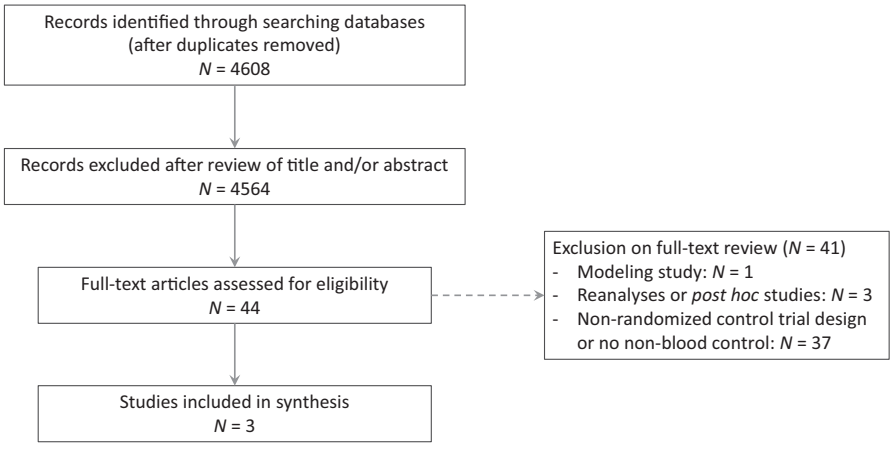

FIGURE 1 Selection of studies for inclusion in review.

TABLE 1 Prehospital civilian transfusion RCTs.

First author (study name)	Location (year)	General inclusion criteria (all were non-arrest adults with trauma)	Total *n* (% died)	Transfusate in PHT arm
Moore[27] (COMBAT)	United States (2018)	Shock defined as SBP < 70 *or* SBP 71–90 with HR > 107	130 (12.3)	Thawed plasma (2 units)
Sperry[16] (PAMPer)	United States (2018)	At least one episode of SBP < 70 *or* SBP < 90 with HR > 108	309[a] (27.8)	Thawed plasma (2 units)
Crombie[28] (RePHILL)	England (2022)	Shock defined as SBP < 90, *or* no radial pulse	423 (43.7)	Up to 2 units each of RBCs and lyophilized plasma

Abbreviations: COMBAT, Control of Major Bleeding After Trauma Trial; HR, heart rate; MA, meta-analysis; PAMPer, Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock; PHT, prehospital transfusion; RBC, red blood cells; RCTs, randomized controlled trials; RePHILL, Resuscitation with Blood Products in Patients with Trauma-related Haemorrhagic Shock Receiving Prehospital Care.
[a]The study *n* as depicted in Table 1 is the patient *n* analyzed for this MA. For PAMPer,[16] this is the *n* of randomized patients in whom the usual-care group was accrued at bases that did not provide RBCs as part of routine care.

TABLE 2 Overall logistics, acuity, and fluid administration highlights in three PHT trials.

Study	Prehospital time[a]	Acuity	Prehospital crystalloid (mL)	Early blood products[a]
Moore[27] (COMBAT)	Median transport time, 16–19 min	Median new ISS: 27	Median higher ($p = 0.02$) in controls (250) vs. CivPHT group (150)	% requiring RBC transfusion within 24 h: 55% (CivPHT group) vs. 58% (control) % requiring plasma transfusion within 24 h: 45% (CivPHT group) vs. 43% (Control)
Sperry[16] (PAMPer)	Median transport time, 40–42 min	Median ISS: 22	Median higher ($p = 0.01$) in controls (900) vs. CivPHT group (500)	% receiving RBC and plasma within 24 h: RBC 55%–58%, plasma 26%–29%
Crombie[28] (RePHILL)	Mean time, randomization to hospital, 35–37 min	Median ISS: 36	Means outside of study intervention were similar in CivPHT (422) and controls (437); as part of study controls received up to 1 L additional crystalloid	Median RBC units and plasma within 24 h were both higher ($p < 0.01$) in CivPHT group (RBC 6.3, plasma 5.0) vs. controls (RBC 4.4, plasma 3.4)

Abbreviations: CivPHT, civilian PHT (intervention group); COMBAT, Control of Major Bleeding After Trauma Trial; ISS, Injury Severity Score; PAMPer, Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock; PHT, prehospital transfusion; RBC, red blood cells; RePHILL, Resuscitation with Blood Products in Patients with Trauma-related Haemorrhagic Shock Receiving Prehospital Care.
[a]Where two numbers are reported (e.g., 40–42) there was no overall combined-group result reported; numbers correspond to the two study groups' results, which were statistically nonsignificant in all instances in which analysis was executed.

trials did not change 1-month mortality findings. For example, RePHILL included Bayesian (rather than frequentist) results based on a range of prior probabilities; effect estimates for CivPHT were 71.2%–88.2% but the credible range included both CivPHT benefit and harm.

MA: relative risk of 1-month mortality with transfusion versus no transfusion

MA results are summarized in Figure 2. The forest plot output includes reporting of favorable *Q* (i.e., failure to reject H_0 of homogeneity at $p = 0.13$) with sufficiently low I^2 (48.5%) to justify pooled effect estimation. For the three studies we assessed, CivPHT was associated with a nonsignificant ($p = 0.38$) improvement in survival (pooled estimate RR 0.87, 95% CI 0.63–1.19).

Extended analyses (plotted and described in detail in the supplement) did not suggest that the MA results were sensitive to bias. Funnel plotting did not rule out small-study bias, but the imputed-study RR was similar (0.87) to the main MA result and the imputed-study RR's 95% CI included the null value. The RR 95% CI also crossed the null in all three omitted-study MAs; depending on which study was excluded the RR ranged from 0.81 to 0.90.

DISCUSSION

This review and MA set out to provide synthesis of available CivPHT evidence. The most important finding was a suggestion of benefit—13% relative reduction in 1-month mortality–that failed to reach statistical significance. Our MA's 95% CI is consistent with RCT trials' data suggesting CivPHT reduces mortality by as much as 37% or increases mortality by up to 19%.

This MA's failure to identify a statistically significant CivPHT benefit is unsurprising, since the reviewed evidence base

TABLE 3 Main findings of $N = 3$ RCTs reviewed.

Study	Control group: *n* lived, *n* died	Transfusion group: *n* lived, *n* died	Risk difference[a] (95% CI)	RR[a] (95% CI)
Moore[27] (COMBAT)	59, 6	55, 10	0.054 (−0.062 to 0.170)	1.54 (0.60–3.98)
Sperry[16] (PAMPer)	98, 50	125, 36	−0.114 (−0.214 to −0.014)	0.662 (0.459–0.954)
Crombie[28] (RePHILL)	120, 99	118, 86	−0.037 (−0.132 to 0.058)	0.94 (0.76–1.17)[b]

Abbreviations: COMBAT, control of major bleeding after trauma trial; PAMPer, prehospital plasma during air medical transport in trauma patients at risk for hemorrhagic shock; RCT, randomized controlled trial; RePHILL, resuscitation with blood products in patients with trauma-related hemorrhagic shock receiving prehospital care; RR, risk ratio.

[a]Directionality: transfusion favored by negative numbers for risk difference numbers or RR < 1.

[b]Results are per RePHILL authors, adjusted for intervention delivery site.

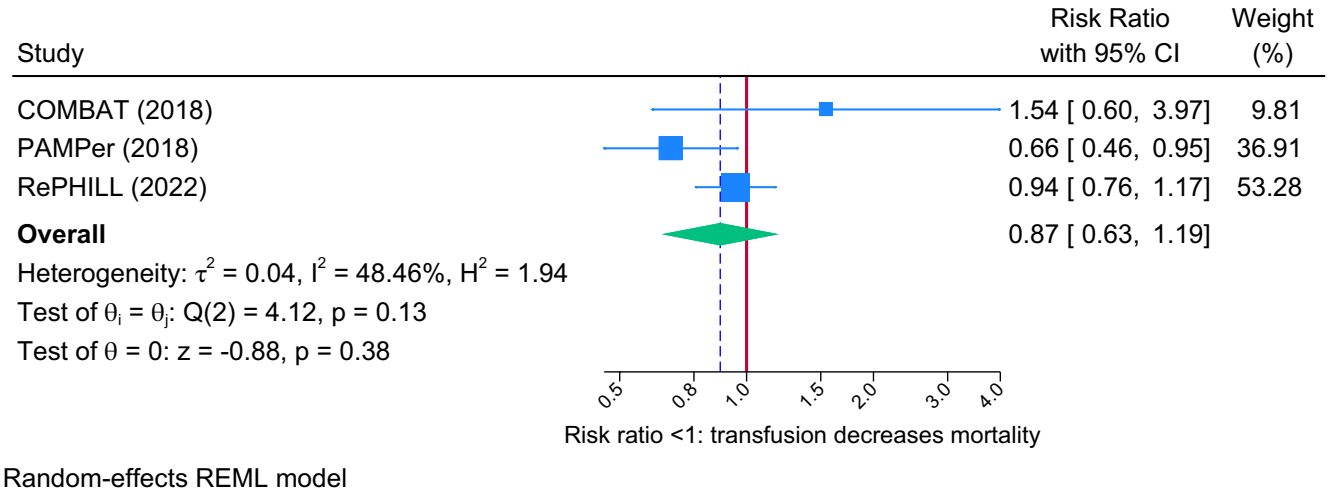

FIGURE 2 Forest plot: mortality RR with transfusion versus no transfusion. RR, risk ratio.

contains only three[16,27,28] controlled CivPHT trials, two of which (COMBAT[27] and RePHILL[28]) failed to demonstrate statistically significant benefit from prehospital administration of blood or blood products. A 2019 MA[19] assessing PAMPer[16] and COMBAT[27] failed to identify a significant CivPHT benefit; the subsequently reported negative findings of RePHILL[28] bolster the case that more RCT data are needed to support a contention that CivPHT improves 1-month survival.

We believe that our most important finding is that CivPHT, a resource-intensive therapy with nonzero risk, has only been assessed in three RCTs—two of which were negative for CivPHT effect on arguably the most patient-centered endpoint of survival to at least 1 month postinjury. The belief that mortality benefit of civilian EMS transfusion is settled science[29] requires revisitation. We do believe that in selected cases—using a selection process not yet fully elucidated—CivPHT is highly likely to improve survival. However, we are not sanguine about the ability to use existing RCT data as a basis for a strong stance favoring widespread CivPHT.

If there are only three RCT CivPHT studies, how should our MA results be framed within the context of the overall EMS transfusion literature? While a detailed review of early transfusion is beyond our scope, two particular sets of studies warrant attention: secondary analyses (of RCT data) and high-level observational cohort study (OCS) data.

Secondary and post hoc reports[21,22,30] from COMBAT and PAMPer have extended these studies' insights into CivPHT. Findings from these reanalyses, which should be viewed as nondefinitive given their methodology, suggest CivPHT benefits for blunt trauma patients[21] of moderate acuity[30] with longer (>20-min) transport times.[22] These important hypotheses are worthy of exploration in future RCTs.

This MA's exclusion of military and non-RCT studies risked excluding potentially high-quality reports. We judged that the issues (and potential controversy) surrounding CivPHT were sufficiently compelling for a MA to include only the highest grade of trial design in civilian populations, but the MA limitation associated with excluding non-RCTs is acknowledged. Particularly with regard to military-setting studies, we advocate using available data from the battlefield to inform civilian clinical care, but we caution that for major endeavors it seems judicious to confirm war-zone clinical lessons with high-quality data from the nonmilitary setting.

We note that there are at least two natural experiment (NE) studies in the CivPHT trauma evidence base. Since NE is the only OCS design that (per GRADE guidance[12,31,32]) can receive a quality rating higher than "low" we mention here the 1-month mortality results of these NE studies.

In 2017 Holcomb et al.[33] employed a propensity-matched NE design to assess CivPHT patients receiving plasma (24%), RBCs (7%), or

both (69%). In their analysis of 109 patients, CivPHT was associated with a nonsignificant ($p=0.75$) mortality reduction with odds ratio (OR) of 0.85 (95% CI 0.32–2.28). Two years later, in a retrospective analysis of 539 patients, Rehn et al.[34] reported statistically nonsignificant ($p=0.65$) mortality reduction (OR 0.92, 95% CI 0.64–1.32) after introducing a CivPHT protocol in the UK.

With our MA pooled effect estimate of a 13% relative risk reduction, there is potential consistency in the NE studies' effect estimates—albeit in mortality OR, which overestimates RR in severely injured patients—of 8%–15% reduction in death odds. The question quickly arises: is the current evidence manifesting Type II error in failing to detect as significant a smaller CivPHT mortality benefit than that for which studies were originally powered?

The question of the degree to which underpowering is problematic in the CivPHT reports is answered easily for COMBAT, which had a point estimate favoring nontransfusion. Similarly, power was not an issue in PAMPer, which identified a significant mortality benefit with CivPHT. For RePHILL, the smaller reduction in RR (6%) was not only nonsignificant; the RePHILL authors calculated that even with as many as 5000 study subjects their CivPHT mortality benefit estimate's 95% CI would include the null value. It is difficult to ascribe to underpowering, negative CivPHT mortality benefit findings either in individual studies or in this MA.

The final issue pertinent to framing this MA's findings in the context of the CivPHT evidence is our nonpresumption of benefit accrued by civilian EMS administration of RBCs. Since the MA goal was to compare CivPHT versus nontransfused controls, we excluded at least three recent high-quality studies[13–15] that assessed addition of blood components to a control group of EMS patients receiving RBCs. We note that none of these three recent studies found statistically significant 1-month mortality improvement by adding (to RBCs) either cryoprecipitate (Davenport et al.,[14] 1-month mortality OR 0.96, 95% CI 0.75–1.23) or plasma (Jost et al.,[15] death hazard ratio 1.07, 95% CI 0.44–2.61; Mitra et al.,[13] RR 0.73 with 95% CI 0.24–2.27).

LIMITATIONS

Although we shared the judgment of previous systematic reviewers[19] that the CivPHT RCTs were of overall high quality, the studies were not without limitations. We consider next some of those limitations, particularly those with relevance to pooled effect estimation.

COMBAT[27] was quite straightforward in its methodology and judged by us to not be subject to substantial overall bias risk. The overriding issue with COMBAT's extrapolation beyond the study center was logistics of the Denver setting. When urban CivPHT is considered in metropolitan areas with short (less than half of RePHILL[28] times) transport times to high-level trauma care and hospital-based transfusion, data simply do not support presumption of a 1-month mortality benefit to EMS transfusion.

One reason for the negative overall finding in this MA may be that the relatively small dose of blood products administered in the EMS setting is insufficient to effect mortality improvement. This shortcoming is most notable for COMBAT, in which approximately a third of patients in the CivPHT group received both fresh-frozen plasma units prior to hospital arrival. The small proportion of the blood products delivered in the prehospital setting may simply be a dose that is too low to reap identifiable benefit. Assessing blood product administration over time—ignoring the place of administration—then the bringing forward of transfusion commencement by minutes (i.e., by having EMS transfusion) may not have an effect in most cases.

The main bias issues pertinent to PAMPer[16] were related to its enrollment and cluster randomization. The practicality of PAMPer methodology is acknowledged and may well have been the factor that enabled this important study to proceed. However, given awareness at the time of decision to enroll a given patient, of that patient's allocation group, there is potential for preferential enrollment of "salvageable" cases into the study's PHT arm. This concern is given weight by the dissimilar study *n* entered into transfused ($n=230$) versus nontransfused ($n=271$) groups. The potential for futility bias, which would be strongly unidirectional in favor of transfusion, has been acknowledged by the study authors and others.[35]

PAMPer also enrolled patients who had received RBCs (either at referring EDs or as part of routine care for HEMS crews). This source of bias—which would be in the direction *against* transfusion benefit if RBCs did in fact improve outcome—was not borne out in PAMPer-reported analyses of heterogeneity of effect: there was no difference in PAMPer findings related to whether RBCs were administered as part of routine prehospital care. Our MA RR calculation for PAMPer's no-RBC cases (RR 0.66, 95% CI 0.46–0.95) was similar to the OR of 0.61 (95% CI 0.40–0.91) reported in PAMPer, for a model adjusted for RBC administration.

PAMPer[16] controls received nearly twice the crystalloid volume as did those receiving CivPHT. However, the aforementioned PAMPer-reported sensitivity analysis demonstrating no change in results dependent on RBC administration also found no results change when the model accounted for prehospital crystalloid volume. This suggests that another potential confounder of CivPHT trials, differing volumes of crystalloid, may not have had a substantial effect on 1-month mortality.

Crystalloid volume is also a potential source of bias in RePHILL,[28] in which non-CivPHT patients received up to 1 L of saline. The RePHILL transfusion group received, on average, 1.57 units (443 mL) of RBCs and 1.25 units (266 mL) of plasma. The control group cases received an average 2.55 units (638 mL) of normal saline by infusion. It is possible that transfusion benefits were diluted by crystalloids' contributing to dilutional coagulopathy. More problematic in RePHILL was the finding that as compared to controls, CivPHT cases received both more RBCs (6.2 units vs. 4.4 units) and more plasma (5.3 units vs. 3 4 units). This could represent a failure of randomization (a conclusion not supported by other RePHILL findings), or the administration of prehospital blood could result in more overall transfusion in the initial 24 h. The CivPHT intervention thus may increase resource use without affecting 1-month mortality.

Since not all regional EMS services participated in RePHILL, there is some question as to whether services' likelihood of joining the study was related to preexisting belief in CivPHT efficacy. This service-level selection issue could bias results in either direction. Overall, in our judgment RePHILL seems to have been characterized by few elements of bias, and the RePHILL methodology and reporting left few unaddressed questions. Reporting included sensitivity analysis as well as Bayesian assessments based on varying prior probabilities.

RePHILL's preplanned sensitivity analyses included apt (given COMBAT findings) subgroup analysis for benefit in different subpopulations (e.g., different acuity, varying transport times). RePHILL's findings remained negative for CivPHT benefit in all of these analyses, thus reducing chance that the study's overall results had been subject to bias or confounding. All sensitivity analyses (including Bayesian calculations) arrived at essentially the same conclusion: an effect estimate of small CivPHT benefit but with 95% CI encompassing the null value.

Apart from any shortcomings of the reviewed studies, this MA has separate limitations. Our definition of "transfusion" combined CivPHT plasma and plasma + RBC studies. We do not believe it likely that all forms of CivPHT have precisely the same 1-month mortality effect—unless that effect is no effect. Combination of different forms of CivPHT into one MA is an acknowledged weakness of this review.

As mentioned with regard to COMBAT, but with relevance to the larger MA results, our review's shortcomings include a grouping of different prehospital systems with different logistics and patient populations (e.g., differing numbers with certain injury patterns, differing baseline mortality). The potential for clinical heterogeneity limits appropriateness of this MA's combining individual study results.

This MA focus on 1-month mortality is another potential weakness of our review. We explicitly designed our study to only assess 1-month mortality because we felt that this was by far the most patient centered endpoint and one that was shared by all three papers with the same definition. Restriction to 1-month mortality isolated an endpoint that was not always the primary endpoint of assessed studies and neglecting other CivPHT-positive endpoints of potential clinical import (e.g., 24-h survival[19]). As others[15] have pointed out, the ultimately elucidated benefit from CivPHT may involve different endpoints, in different populations.

In addition to restricting our endpoint focus on one positive endpoint, we also did not assess "negative" endpoints such as risks or costs. We note an earlier MA[19] of two trials found no increased risk of acute lung injury or multiorgan failure, and the trial (RePHILL) published since that earlier MA also found no additional CivPHT risk other than perhaps increased early blood product use.

With regard to negative effects of CivPHT, we conclude that, outside of its resource-intensive nature (a subject beyond scope of this review), CivPHT does not appear to pose significant risks to patients in terms of short-term complications. Transport times were not prolonged.[27] There was no increase in adverse events in a variety of assessed parameters such as thrombotic events[27] or acute lung injury.[27] The RCTs did not assess long-term complications such as alloimmunization in the case of CivPHT of Rh-positive blood to Rh-negative females of childbearing age. No conclusions on these complications should be drawn based on the RCTs' data.

In our judgment, the most striking limitation of this MA was the low study *N*. The identification of only three RCTs of CivPHT had methodologic ramifications. We had insufficient *N* for robust evaluation of heterogeneity, and we were unable to execute important assessments (e.g., meta-regression) that could have clarified any beneficial role for EMS transfusion. We were also not able to calculate a prediction interval for likely benefit ranges of future studies. Additionally, we did not execute formal analysis of adverse events due to low study *N*, low *N* of major adverse events, and lack of clear reporting or even attribution of adverse events in the included studies. A MA of only three studies may be informative, but it is certainly not definitive.

The above point leads to perhaps the most critical facet of the CivPHT debate: the paucity of evidence supporting 1-month mortality improvement from *any* form of CivPHT. In the hospital setting, RCTs comparing various forms of early transfusion have been reported for over a decade.[36] But largely due to methodologic challenges (e.g., ethics review, randomization), the prehospital evidence base has remained sparse.

One 2014 RCT had low enrollment and ceased without collecting usable evidence (Pre-Hospital Use of Plasma for Traumatic Hemorrhage, clinicaltrials.gov 02303964). Newer ongoing trials such as PRIEST (Prehospital Transfusion Strategy in Bleeding Patients, clinicaltrials.gov 04879485) and TOWAR focus on which form of CivPHT is preferable.

Determination of which components are preferred is crucial to advancement of CivPHT. However, our MA *N* suggests that there is still room (and clinical equipoise) for evaluation of CivPHT versus a nontransfused control group. Since the main difficulty in applying CivPHT is identifying which patients will benefit, the imprecision in prehospital triage to blood products could explain in part (or in whole) the failure to identify a benefit to CivPHT. There are many areas for future RCTs. Examples include focus on higher patient acuity, specific injury patterns (e.g., head injury), and assessment of a dose–response transfusion effect. Equally helpful would be RCTs that control (limit) the amount of crystalloid infused.

CONCLUSIONS

In conclusion, our main finding was the lack of definitive evidence that civilian prehospital transfusion is associated with improved 1-month mortality. The failure to identify such benefit in this meta-analysis—which finding does not translate into a definitive demonstration that civilian prehospital transfusion is not occasionally lifesaving—should give pause to emergency medical services systems moving forward with widespread civilian prehospital transfusion programs based on an assumption of lifesaving effects of early blood products. Further studies should focus not only on

which formulations of blood products improve outcomes, but trials should also focus on which patients are most likely to benefit from any form of civilian prehospital transfusion.

AUTHOR CONTRIBUTIONS

David W. Schoenfeld and Stephen H. Thomas substantially contributed to the conception and design of the work, systematic review, interpretation, drafting, and revision. Stephen H. Thomas also contributed significantly to the statistical analysis. Carlo L. Rosen and Tim Harris provided substantial contributions in the systematic review, interpretation, drafting, and revision.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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