The Use of Central Venous to Arterial Carbon Dioxide Tension Gap for Outcome Prediction in Critically Ill Patients: A Systematic Review and Meta-Analysis

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Objectives: In this systematic review and meta-analysis, we assessed whether a high Co_2 gap predicts mortality in adult critically ill patients with circulatory shock.

Data Sources: A systematic search of MEDLINE and EMBASE electronic databases from inception to October 2019.

Study Selection: Studies from adult (age ≥ 18 yr) ICU patients with shock reporting Co_2 gap and outcomes of interest. Case reports and conference abstracts were excluded.

Data Extraction: Data extraction and study quality assessment were performed independently in duplicate.

Data Synthesis: We used the Newcastle-Ottawa Scale to assess methodological study quality. Effect sizes were pooled using a random-effects model. The primary outcome was mortality (28 d and hospital). Secondary outcomes were ICU length of stay, hospital length of stay, duration of mechanical ventilation, use of renal replacement therapy, use of vasopressors and inotropes, and association with cardiac index, lactate, and central venous oxygen saturation.

Conclusions: We included 21 studies (n = 2,155 patients) from medical (n = 925), cardiovascular (n = 685), surgical (n = 483), and mixed (n = 62) ICUs. A high Co_2 gap was associated with increased mortality (odds ratio, 2.22; 95% CI, 1.30–3.82; p = 0.004) in patients with shock, but only those from medical and surgical ICUs. A high Co_2 gap was associated with higher lactate levels (mean difference 0.44 mmol/L; 95% CI, 0.20–0.68 mmol/L; p = 0.0004), lower cardiac index (mean difference, −0.76 L/min/m^2; 95% CI, −1.04 to −0.49 L/min/m^2; p = 0.00001), and central venous oxygen saturation (mean difference, −5.07; 95% CI, −7.78 to −2.37; p = 0.0002). A high Co_2 gap was not associated with longer ICU or hospital length of stays, requirement for renal replacement therapy, longer duration of mechanical ventilation, or higher vasopressors and inotropes use. Future studies should evaluate whether resuscitation aimed at closing the Co_2 gap improves mortality in shock. (*Crit Care Med* 2020; XX:00–00)

Key Words: critical illness; microcirculation; resuscitation; shock; systematic review; venoarterial carbon dioxide tension gap

In critically ill patients, circulatory shock comprises up to one third of all ICU admissions and is associated with more than 50% mortality (1). Ischemia and tissue hypoxia due to macro- and microcirculatory failure are the hallmarks of shock and require prompt recognition and timely resuscitation in order to halt the cascade of multiple organ dysfunction and death (2, 3). The current resuscitation paradigm focuses primarily on restoring the macrocirculation more so than the microcirculation. This is largely because macrocirculatory variables can be readily assessed using hemodynamic monitors and point-of-care ultrasound. Monitoring of the microcirculation, however, remains elusive. Biochemical markers such as lactate or central venous oxygen saturation ($Scvo_2$) are commonly used as crude surrogates for the adequacy of tissue perfusion and in guiding resuscitative efforts (4–6). However, mortality from shock remains high, despite the widespread adoption of interventions aiming at normalizing these variables. This calls into question whether additional markers of microcirculatory function may be of greater prognostic and therapeutic value (7, 8).

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The Co_2 gap, defined as the difference between venous and arterial carbon dioxide tensions, is a novel marker of shock that reflects microcirculatory function (9). After establishing arterial and venous access, measuring the Co_2 gap can be easily and expediently performed at the bedside. Current evidence suggests that a Co_2 gap of greater than 6 mm Hg predicts poor outcomes in septic shock (10). In addition, a persistently high Co_2 gap at 24 hours after ICU admission is associated with higher mortality despite normalization of lactate levels (11, 12). A recent systematic review of patients with septic shock found that a high Co_2 gap was associated with impaired hemodynamics, tissue perfusion markers, and increased rates of death (13). Whether the same is true for all shock patients is unknown.

In this systematic review and meta-analysis, we assessed whether a high Co_2 gap predicts poor outcomes in critically ill patients from medical, surgical, and cardiovascular ICUs presenting with circulatory shock. We examined the association between a high gap and mortality (primary outcome), ICU length of stay (LOS), hospital LOS, mechanical ventilation days, need for inotropes and vasopressors, and need for renal replacement therapy (RRT) (**Fig. 1**). Building on the premise that a high Co_2 gap predicts mortality despite normalization of lactate in septic shock patients (11, 12), a high gap (as a marker of microcirculatory failure) may carry therapeutic implications in all shock patients. This may constitute an important step in establishing Co_2 gap as a clinical marker for "underresuscitation" and determining whether interventions aimed at closing the gap can improve clinical outcomes.

MATERIALS AND METHODS

Search Strategy

We conducted a systematic search of the MEDLINE and EMBASE electronic databases, using the OvidSP search interface, from inception through October 2019. The search was performed by a clinical librarian with training in search strategies for systematic reviews. We included studies in adult humans (age ≥ 18 yr) published in the English language. Studies conducted in the pediatric population and animal studies were excluded. To identify all relevant studies, a search strategy using combinations of controlled vocabulary (subject headings) and keywords was adopted. This comprised the following search terms: "CO2 gap," "DELTAPCO2," "dPCO2," "pCO2 gradient," "CO2 difference," "PV-ACO2," "resuscitation," "critical care," "intensive care units," "critical illness," "trauma," "sepsis," "septic shock," "perioperative," "postoperative" period, and "surgery."

The search strategies were modified for each database to include database-specific descriptors and field names. Reference lists of relevant studies were hand-searched to identify additional published studies that met our inclusion criteria. A detailed description of our search strategy is included in Supplemental Digital Content - Search Strategy (found in Supplemental Digital Content 1, http://links.lww.com/CCM/F814).

Two reviewers (Z.D., R.L.) independently screened titles and abstracts to identify articles for full review. They further evaluated the full text of potentially eligible studies, based on predetermined eligibility criteria. Disagreements between reviewers were resolved by discussion, consensus, and, when necessary, adjudication by a third reviewer (M.S.).

Study Selection

No restrictions were imposed regarding study design. Studies were eligible for inclusion if they: 1) enrolled adult (age ≥ 18 yr) critically ill patients with shock from medical, surgical, and cardiac ICUs; 2) measured the Co_2 gap; and 3) reported any of the following variables: 28-day mortality; hospital mortality; ICU and/or hospital LOS; ICU severity of illness scores (the Sequential Organ Failure Assessment [SOFA] and Acute Physiology and Chronic Health Evaluation [APACHE] II scores); duration of mechanical ventilation; frequency of requiring RRT; and association of the Co_2 gap with lactate levels, $Scvo_2$, or cardiac indices. Case reports and conference abstracts were excluded.

Data Extraction

Two reviewers (Z.D., K.F.) independently and in duplicate extracted pertinent data from all studies utilizing a predesigned data extraction form. Variables of interest included study design, patient demographics, hemodynamic variables, standard tissue perfusion markers, and study outcomes. Disagreements were resolved by discussion, consensus, and, when necessary, consultation with a third reviewer (M.S.).

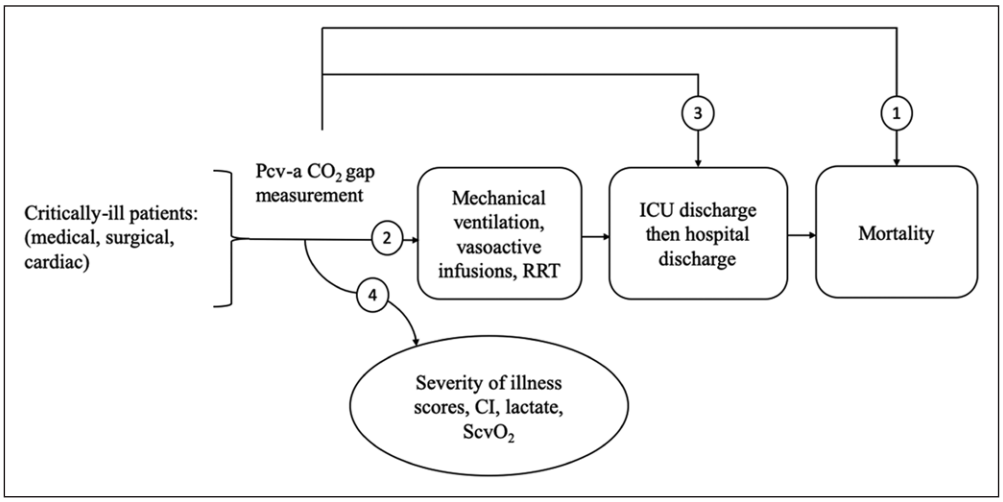

Figure 1. Analytic framework to assess the Pcv-aCo_2 gap with different outcome variables. Pcv-aCo_2 = central venous to arterial partial pressure of Co_2, RRT = renal replacement therapy, $Scvo_2$ = central venous oxygen saturation.

Methodologic Quality Assessment

The Newcastle Ottawa regulations coding manual and assessment scale was used to evaluate study quality and risk of bias. Two reviewers (Z.D.,

R.L.) independently assessed risk of bias in all eligible studies and disagreements were resolved by discussion and consensus.

Statistical Analysis

The Co_2 gap was analyzed as a dichotomous predictor; high (≥6 mm Hg) versus low (<6 mm Hg). The primary outcome was mortality (28 d and hospital). Secondary outcomes were ICU LOS, hospital LOS, duration of mechanical ventilation, use of RRT, and use of vasopressors and inotropes. We also examined the association of a high Co_2 gap with standard resuscitation markers (cardiac index, lactate, and $Scvo_2$).

For dichotomous outcomes, odds ratios (ORs) with 95% CIs were used to measure association with a high Co_2 gap. Mean differences (MDs) with 95% CI were used to measure association between a high Co_2 gap and continuous outcomes. For all outcomes, random-effect estimates were computed based on the DerSimonian and Laird method of moments. For studies that reported continuous data as medians and interquartile ranges, sample means and sds were estimated using the methods described by Wan et al (14).

Random-effects meta-analyses were performed on all studies, then a sensitivity analysis was performed limiting the results to studies with low risk of bias. Statistical heterogeneity was assessed using the Cochran's Q statistic and I^2, which describes the percentage of variability in the estimates that is due to true effect heterogeneity rather than sampling error. We considered study-level estimates to be statistically heterogeneous if the I^2 statistic was greater than 75%. To explore effects by population, studies performed in the medical, surgical, and cardiac surgical populations were analyzed as subgroups. To control for the known effects of SOFA and APACHE II scores on mortality, meta-regression was performed utilizing Knapp-Hartung random-effects weights assigned to MDs in scores between the high and low Co_2 gap groups. All p values were from two-sided tests and results were deemed statistically significant at p value of less than or equal to 0.05.

Forest plots were created to show individual study results and summary effect estimates. Publication bias was assessed by visual examination of funnel plots. Further, imputation of potentially unpublished studies was performed to assess for the effects of publication bias on our results. Comprehensive Meta-Analysis (Version 3.0; Biostat Inc, Englewood, NJ) was used for statistical analysis and Review Manager (RevMan Version 5.3; The Cochrane Collaboration, London, United Kingdom, 2014) was used for producing risk of bias summaries and graphs.

RESULTS

The search yielded a total of 2,466 studies prior to removal of 730 duplicates. After screening titles and abstracts, another 1,489 out of the remaining 1,736 studies were excluded. Another 226 studies were subsequently excluded following full-text review. The remaining 21 studies underwent data extraction and quantitative analysis (**Fig. 2**).

All studies (k = 21) were observational by design. The majority of studies were from medical ICUs (k = 12), followed by cardiac (k = 4), surgical (k = 4), and mixed (k = 1) ICUs. All studies measured the Co_2 gap at admission to ICU and considered this as the baseline or time zero value except three studies. Two studies considered the baseline Co_2 gap value once the pulmonary artery catheter was inserted (9, 15), and the other study considered the baseline value within 24 hours from ICU admission (16). Characteristics of the included studies are summarized in **Supplemental Digital Content—Table 1** (Supplemental Digital Content 2, http://links.lww.com/CCM/F815) and **Supplemental Digital Content—Table 2** (Supplemental Digital Content 3, http://links.lww.com/CCM/F816).

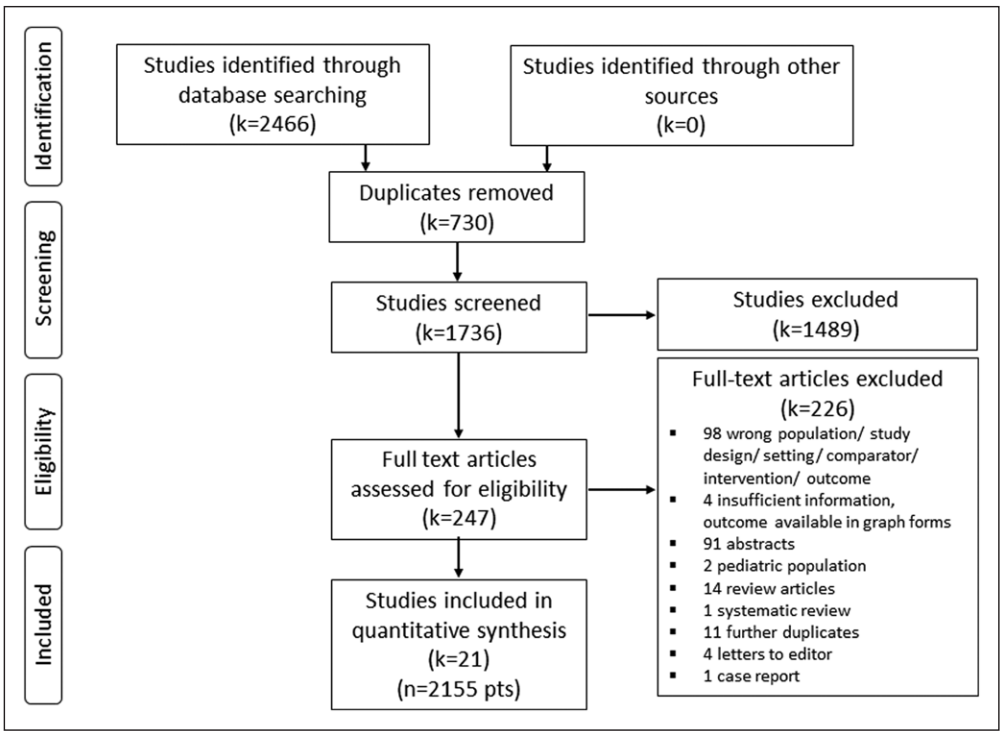

Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram depicting the study selection process.

Association of the Co_2 Gap With Mortality

Thirteen studies examined the association of a high Co_2 gap with mortality (in-hospital or at 28 d) comprising a total of 1,534 patients. A random-effects meta-analysis of all studies showed that a high Co_2 gap was associated with an OR of death of 2.22 (95% CI, 1.30–3.82; p = 0.004) (**Fig. 3**). These results were robust to a sensitivity analysis based on study quality. Restricting the analysis to good quality studies only, a high Co_2 gap remained associated with a statistically significant OR of death

of 2.32 (95% CI, 1.31–4.12; $p = 0.004$). Statistical heterogeneity was moderate (I^2 of 59%; Cochran's Q statistic $p = 0.005$) (**Supplemental Digital Content—Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCM/F814).

To explore the observed heterogeneity in effect sizes, we carried out a subgroup analysis by study population. This revealed a high Co_2 gap to be a strong predictor of mortality in medical (OR, 2.92; 95% CI, 2.02–4.24; $p = 0.000001$) and surgical (OR, 8.02; 95% CI, 1.82–35.28; $p = 0.01$) ICU patient populations (**Supplemental Digital Content—Figs. 2** and **3**, Supplemental Digital Content 1, http://links.lww.com/CCM/F814). However, the results from the surgical subset of patients should be interpreted with caution given the paucity of studies and wider CIs. In contrast to medical and surgical studies, a high Co_2 gap was not associated with an increased OR of death in cardiac surgery patients (OR, 0.25; 95% CI, 0.04–1.47; $p = 0.13$ and **Supplemental Digital Content—Fig. 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/F814).

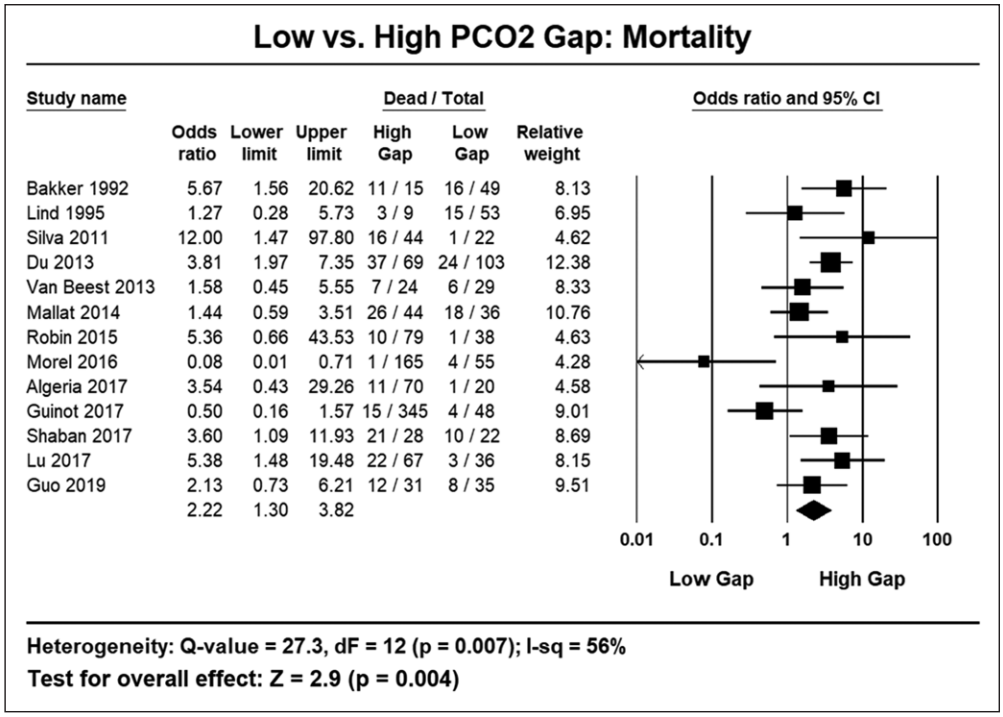

Figure 3. Hospital or 28-d mortality comparison between high Co_2 gap versus low Co_2 gap. *df* = degrees of freedom.

Association of the Co_2 Gap With Standard Hemodynamic and Tissue Perfusion Markers

At admission to the ICU, high Co_2 gap was associated with elevated lactate levels (MD, 0.44 mmol/L; 95% CI, 0.20–0.68 mmol/L; $p = 0.0004$) (**Fig. 4**), lower cardiac index (MD, –0.76 L/min/m^2; 95% CI, –1.04 to –0.49 L/min/m^2; $p = 0.00001$) (**Supplemental Digital Content—Fig. 5**, Supplemental Digital Content 1, http://links.lww.com/CCM/F814), and lower $Scvo_2$ (MD, –5.07; 95% CI, –7.78 to –2.37; $p = 0.0002$).

Predictive Power of the Co_2 Gap Adjusting for Severity of Illness Scores

Meta-regression showed that there is an insufficient evidence to suggest that Co_2 gaps adds to the predictive power of the SOFA ($p = 0.19$; $R^2 = 0.36$) and APACHE II scores ($p = 0.78$; $R^2 = 0$) (**Supplemental Digital Content—Figs. 6** and **7**, Supplemental Digital Content 1, http://links.lww.com/CCM/F814).

Association of the Co_2 Gap With Other Secondary Endpoints

An elevated Co_2 gap was not associated with ICU LOS (MD, –0.25 d; 95% CI, –0.64 to 0.14 d; $p = 0.21$), hospital LOS (MD, 2.56 d; 95% CI, –1.13 to 6.26 d; $p = 0.17$), requirement for RRT (OR, 1.52; 95% CI, 0.75–3.08; $p = 0.25$) (**Fig. 5**), and longer mechanical ventilation duration in the ICU (MD, 1.59 d; 95% CI, –0.66 to 3.84; $p = 0.17$) (**Supplemental Digital Content—Figs. 8–10**, Supplemental Digital Content 1, http://links.lww.com/CCM/F814). In addition, there were no differences in vasopressor or inotropic support requirements between the high and low Co_2 gap groups, respectively (OR, 1.77; 95% CI, 1.00–3.15; $p = 0.05$) and (OR, 1.28; 95% CI, 0.68–2.40; $p = 0.44$) (**Supplemental Digital Content—Figs. 11** and **12**, Supplemental Digital Content 1, http://links.lww.com/CCM/F814).

Risk of Bias Assessment

Seventy-five percent of studies were determined to be of good overall quality (Risk of Bias Graph: **Supplemental Digital Content—Fig. 13**, Supplemental Digital Content 1, http://links.lww.com/CCM/F814). A breakdown of each individual study's risk of bias per domain is shown in a risk of bias summary plot (**Supplemental Digital Content—Fig. 14**, Supplemental Digital Content 1, http://links.lww.com/CCM/F814).

Assessment of Publication Bias

Funnel plot triangle inspection revealed no evidence of publication bias (**Supplemental Digital Content—Fig. 15**, Supplemental Digital Content 1, http://links.lww.com/CCM/F814). To account for the potential influence of unpublished studies on the point estimate, study imputation was performed. Even after imputation, the log OR for increased mortality remained statistically significant (log OR, 1.85; 95% CI, 1.08–3.16). Publication bias is therefore unlikely to have played a role in our results.

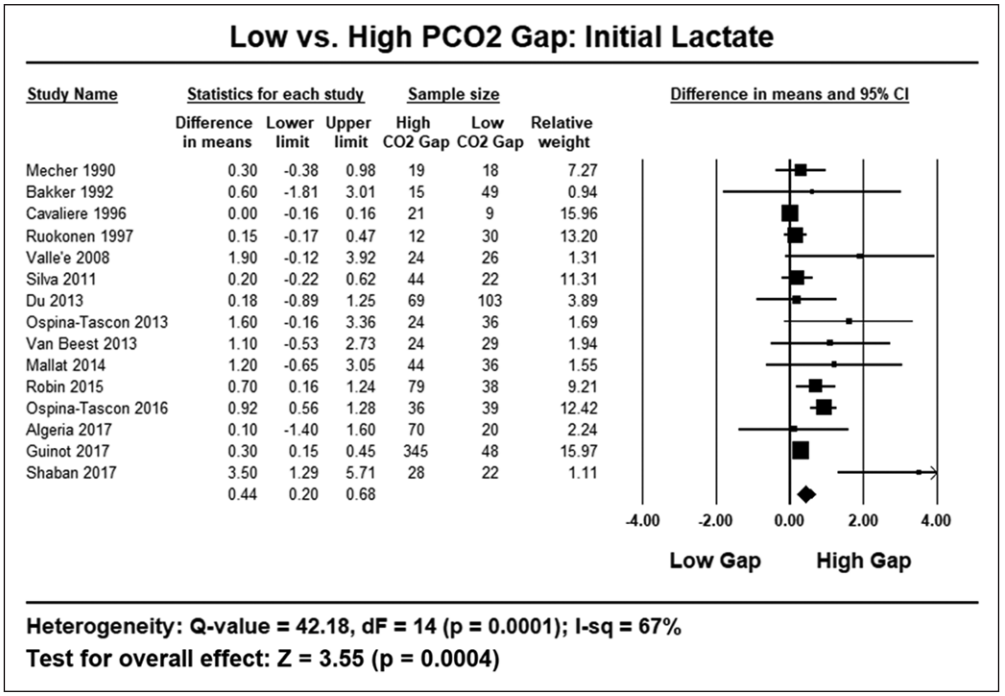

Figure 4. Serum lactate level comparison between the high Co_2 gap versus low Co_2 gap groups. *df* = degrees of freedom.

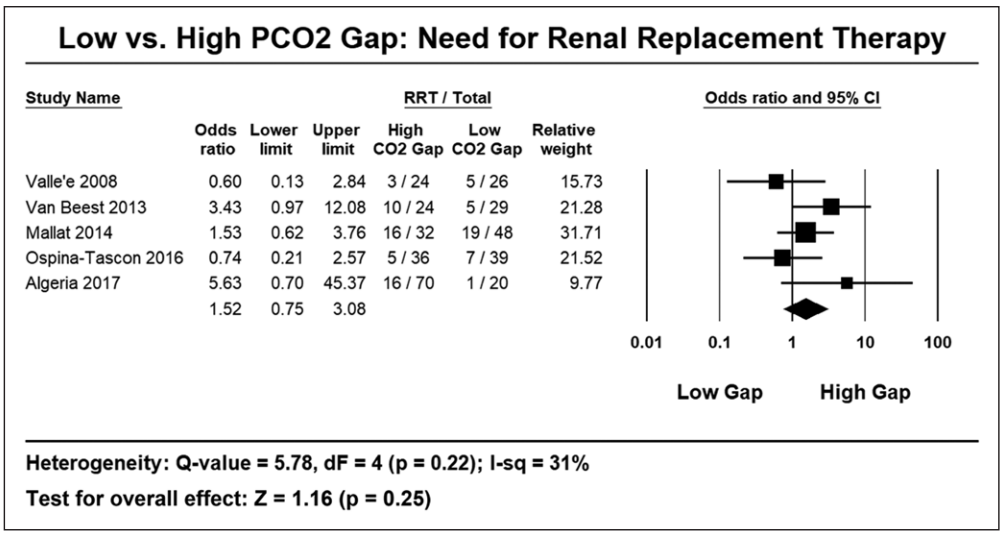

Figure 5. Renal replacement therapy (RRT) requirement between high Co_2 gap versus low Co_2 gap groups. *df* = degrees of freedom.

DISCUSSION

Our systematic review and meta-analysis examined whether a high Co_2 gap predicts clinical outcomes in critically ill patients from medical, surgical, and cardiovascular ICUs presenting with circulatory shock. Our results show that a high Co_2 gap is associated with an increased odds of mortality (at 28 d or in-hospital) in the medical and surgical, but not in the cardiovascular ICU populations. Furthermore, high Co_2 gap was associated with higher lactate levels, lower cardiac index, and lower $Scvo_2$. There was insufficient evidence to suggest that increased Co_2 gap could add to the predictive power of SOFA and APACHE II scores, but this analysis was underpowered due to the small number of included studies. There were no associations between high Co_2 gap and the use of vasopressors and inotropes, RRT requirement, duration of mechanical ventilation, nor ICU and hospital LOS.

A previous systematic review examined this question in patients with severe sepsis and septic shock, demonstrating an association between high Co_2 gaps and 28-day or in-hospital mortality (13). Our study adds to this evidence by demonstrating that high Co_2 gap is associated with an increased odds of mortality in all medical and surgical ICU patients, but not in the cardiovascular ICU patients. The lack of association between Co_2 gap and mortality in cardiovascular patients likely reflects the difference in the underlying pathophysiology of shock and overall lower mortality in this patient population. Microcirculatory dysfunction is common in both cardiopulmonary bypass and off-pump cardiac surgery and may be related to anesthesia, but it appears to be transient and tends to resolve with time reaching close to baseline levels at 24 hours after surgery (17, 18). In general, the mortality in cardiac surgery patients is lower (3.4–6.5%), in part due to advances in surgical techniques and careful patient selection processes (19, 20). In contrast, septic shock patients in the medical and surgical ICUs have high mortality rates of up to 46% (21) that are associated with severe and persistent microvascular dysfunction (9).

The association between Co_2 gap and perfusion markers in our study can be explained by reviewing the physiologic basis of the Co_2 gap (22). The minute flux of metabolically produced Co_2 (Vco_2) is the product of cardiac output (CO) and the difference between Co_2 content of venous blood ($Cvco_2$) and Co_2 content of arterial blood ($Caco_2$) (Equation 1). Solving this equation for CO shows that at steady-state Vco_2 CO is inversely proportional to the venoarterial difference in Co_2 content (Equation 2).

$$\dot{V}CO_2 = CO \times \left(CvCO_2 - CaCO_2\right) \quad (1)$$

$$CO = \frac{\dot{V}CO_2}{CvCO_2 - CaCO_2} \quad (2)$$

The relationship between Co_2 content and Pco_2 is curvilinear (23) and is affected by oxygen levels due to Haldane effect (24), but for clinical purpose, the differences in partial pressure of Co_2 can closely approximate the difference in Co_2 content (22, 25, 26). It is therefore not surprising that in clinical studies Co_2 gap is closely associated with CO or index (10, 25, 26), which was also the case in our study.

While Co_2 gap was associated with lower $Scvo_2$ in our study, it may offer an advantage over oxygen-based indices of hypoperfusion. Combination of Co_2 gap and $Scvo_2$ is a better predictor of mortality than $Scvo_2$ alone (27), while persistently elevated Co_2 gap identifies under resuscitated shock patients with lower cardiac indices despite normalization of $Scvo_2$ (28). One explanation for this superiority of the Co_2 gap is the higher solubility of Co_2 in plasma compared with oxygen, which facilitates its more effective diffusion out of tissues and into the venous blood during states of impaired diffusion (e.g., tissue edema) (22).

Elevated lactate levels are commonly used as a marker of impaired tissue perfusion in shock and are associated with increased mortality (29, 30). It is therefore not surprising that in our study high Co_2 gap was associated with elevated lactate levels. However, given that lactate levels may be affected by factors other than tissue hypoperfusion (31), the Co_2 gap may present a more direct way to assess tissue hypoperfusion in shock. Furthermore, in situations where both lactate and $Scvo_2$ are either normal or confounded, Co_2 gap may identify patients with microcirculatory impairment (32), especially since it was recently shown to correlate with microcirculation indices in early stages of shock resuscitation (9).

The strengths of our systematic review include our emphasis on clinically important outcomes, our adjustment for differences in severity of illness scores, and our assessment of outcomes across different ICU patient subgroups. In addition, the strength of our conclusions was supported by their robustness to sensitivity analysis (limiting the analysis to good quality studies did not impact the results). Limitations include the observational nature of the included studies and the paucity of good quality studies in the surgical and cardiac surgery populations. Furthermore, the definition of high Co_2 gap varied slightly between studies (>5-7 mm Hg) (Supplemental Digital Content—Table 1, Supplemental Digital Content 2, http://links.lww.com/CCM/F815; and Supplemental Digital Content—Table 2, Supplemental Digital Content 3, http://links.lww.com/CCM/F816). Finally, prior studies included in our meta-analysis have demonstrated that persistence of high Co_2 gap or increase in the Co_2 gap with time is associated with worse lactate and SOFA scores, impairment in microcirculation, and higher mortality (9, 10, 15). However, we were unable to meta-analyze these data due to the lack of individual patient data, heterogeneity of Co_2 gap time points, and outcomes between studies.

CONCLUSIONS

In medical and surgical ICU patients presenting with shock, a high Co_2 gap is associated with increased odds of 28-day and hospital mortality. In addition, the high Co_2 gap was associated with higher lactate levels, lower cardiac index, and lower $Scvo_2$. Future studies should evaluate whether resuscitation aimed at "closing" the Co_2 gap improves these clinical outcomes in medical and surgical ICU patients presenting with shock.

Drs. Al Duhailib and Slessarev had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Al Duhailib, Ms. Priestap, Ms. Iansavichene, and Dr. Slessarev involved in concept and design. Drs. Al Duhailib, Hegazy, and Slessarev involved in drafting of the article. Dr. Hegazy and Ms. Priestap involved in statistical analysis. All authors involved in acquisition, analysis, or interpretation of data; critical revision of the article for important intellectual content; and final approval of the article.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

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