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MAJOR ARTICLE

Association Between Cytomegalovirus Reactivation and Clinical Outcomes in Immunocompetent Critically Ill Patients: A Systematic Review and Meta-Analysis

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Background. The aim of our systematic review was to investigate the association between cytomegalovirus (CMV) reactivation and outcomes in immunocompetent critically ill patients.

Methods. We searched electronic databases and gray literature for original studies and abstracts published between 1990 and October 2016. The review was limited to studies including critically ill immunocompetent patients. Cytomegalovirus reactivation was defined as positive polymerase chain reaction, pp65 antigenemia, or viral culture from blood or bronchoalveolar lavage. Selected patient-centered outcomes included mortality, duration of mechanical ventilation, need for renal replacement therapy (RRT), and nosocomial infections. Health resource utilization outcomes included intensive care unit and hospital lengths of stay.

Results. Twenty-two studies were included. In our primary analysis, CMV reactivation was associated with increased ICU mortality (odds ratio [OR], 2.55; 95% confidence interval [CI], 1.87–3.47), overall mortality (OR, 2.02; 95% CI, 1.60–2.56), duration of mechanical ventilation (mean difference 6.60 days; 95% CI, 3.09–10.12), nosocomial infections (OR, 3.20; 95% CI, 2.05–4.98), need for RRT (OR, 2.37; 95% CI, 1.31–4.31), and ICU length of stay (mean difference 8.18 days; 95% CI, 6.14–10.22). In addition, numerous sensitivity analyses were performed.

Conclusions. In this meta-analysis, CMV reactivation was associated with worse clinical outcomes and greater health resource utilization in critically ill patients. However, it remains unclear whether CMV reactivation plays a causal role or if it is a surrogate for more severe illness.

Keywords. cytomegalovirus; immunocompetent; intensive care unit; meta-analysis; systematic review.

It is estimated that 40% to 100% of immunocompetent adults are cytomegalovirus (CMV) seropositive globally [1]. In Canada, the seroprevalence ranges between 60% and 80% [2]. Most primary infections occur in childhood and are subclinical or present with nonspecific symptoms. Cytomegalovirus subsequently remains latent in monocytes and macrophages [3]. This state of latency allows CMV to reactivate when host defenses become compromised, such as in critical illness. Cytomegalovirus reactivation in critically ill patients is well recognized with as high as 71% incidence [4]. The consequences of CMV reactivation in immunocompromised patient populations, such as those with solid organ transplants, have been well described [5]. However, the clinical significance in immunocompetent patients remains controversial. Some postulate viral pathogenesis. Others have suggested that CMV reactivation is only a marker of illness severity [4].

Since the 1990s, several studies have investigated the association between CMV reactivation and outcomes in critically ill patients. In 1990, Domart et al [6] examined patients with mediastinitis after cardiac surgery who were CMV infected, defined by blood and/or urine viral cultures. They showed a significant increase in mortality and hospital length of stay (LOS) compared with CMV-uninfected patients. Thereafter, other studies have also reported increased mortality [7, 8], increased duration of mechanical ventilation [9, 10], increased length of intensive care unit (ICU) stay [11, 12], and increased incidence of nosocomial infections [13]. Contrasting these data, other authors [14, 15] failed to demonstrate a difference in mortality in patients with CMV DNAemia.

With a growing number of studies examining the association between CMV reactivation and ICU outcomes, as well as discrepancies in the available data, systematic reviews and meta-analyses have been previously undertaken. In 2009, Osawa et al [16] conducted the first systematic review on the subject,

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including 13 studies. Four studies reported data on duration of mechanical ventilation, all of which showed longer durations of ventilation in patients with CMV reactivation; however, these data were not meta-analyzed. All but 2 of the included studies reporting death showed no association between CMV reactivation and mortality [16]. In contrast, Kalil et al [17] published a meta-analysis including 8 studies and 633 patients showing a 2-fold increase in the odds ratio of death with CMV infection. However, other clinical outcomes were not examined. These authors updated their results after Heininger et al [14]. Given their discordant results, however, the association between CMV infection and mortality remained significant [18]. Finally, Coisel et al [19] performed a prospective outcomes study of CMV-infected mechanically ventilated patients in which they included a meta-analysis demonstrating increased mortality in patients with CMV antigenemia. Since the publication of this last meta-analysis, at least 4 additional studies have been published on this topic with varying results [15, 20–22].

Considering the availability of new evidence and the absence of meta-analyses examining important outcomes such as duration of mechanical ventilation, ICU LOS, or incidence of nosocomial infection, we conducted this systematic review and meta-analysis to explore the association between CMV reactivation and clinical outcomes in immunocompetent critically ill patients.

METHODS

The protocol of this systematic review has been previously published [23] and was registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD-42016035446).

Objectives

The aim of our systematic review was to explore the association between CMV reactivation (defined by positive pp65 CMV antigen testing, CMV quantitative nucleic acid testing [NAT], or viral culture in either blood or bronchoalveolar lavage) and patient-centered outcomes (including mortality, duration of mechanical ventilation, nosocomial infections, and receipt of renal replacement therapy [RRT]) or health services utilization (ICU LOS, hospital LOS) in immunocompetent critically ill patients.

Data Searches

In brief, the search strategy was developed in consultation with an expert librarian (R.F.). Electronic databases including Ovid MEDLINE, Ovid EMBASE, and the Cochrane Library (including the Cochrane Database of Systematic Reviews and the Cochrane Central Register of Controlled Trials [CENTRAL]) were searched for 3 broad domains: cytomegalovirus, intensive care unit, and sepsis. Search results were restricted to papers published after 1990 and in English or French languages. Relevant conference proceedings (see protocol for details) from the past 2 years and www.clinicaltrials.gov were also screened. Supplementary Appendix 1 presents the complete search strategy.

Study Selection

We included randomized trials, observational studies (either retrospective or prospective), or case-control studies that reported on CMV reactivation in immunocompetent adults ≥18 years old (ie, we specifically excluded solid organ or bone marrow transplant patients, those with advanced human immunodeficiency virus/acquired immune deficiency syndrome or those receiving cytotoxic therapies) and at least 1 patient-centered outcome (mortality, duration of mechanical ventilation, nosocomial infections, RRT) or measure of health resource utilization (ICU and hospital lengths of stay). Two authors (P.L. and J.C.) identified potentially eligible articles after independent review. Any disagreements were resolved through discussion and/or arbitration by the senior author (W.I.S.).

Data Extraction

Data were abstracted from relevant studies by the same 2 authors (P.L. and J.C.) using a standardized electronic data collection form. Additional or missing data, where relevant, were requested from primary authors of included studies on up to 3 attempts. Extracted data included publication-related information, design and quality assessment, inclusion and exclusion criteria, and the method of CMV detection. Demographic and clinical characteristics of the study populations, as well as patient-related and health resource use outcomes, were also included. Supplementary Appendix 2 provides a complete list of all data variables collected. Study methodological quality was rated using the Newcastle-Ottawa Scale [24] for observational and case-control studies.

Outcomes

Our primary outcome was ICU mortality. Secondary outcomes included overall mortality (a combination of 28-day, 30-day, hospital, and long-term mortality), duration of mechanical ventilation, nosocomial infections, need for RRT, vasopressor days, and ICU and hospital lengths of stay.

Analysis

Pooled effect estimates of the association between CMV reactivation and patient-centered outcomes and health service use were calculated. We assessed and quantified statistical heterogeneity for each pooled estimate using the I^2 statistic. Pooled analyses were performed using random effects models (Mantel-Haenszel method) and reported as odds ratios (ORs) with 95% confidence intervals (CIs) for categorical variables and weighted mean differences with 95% CIs for continuous variables. Sensitivity analyses were explored for the primary outcome of ICU mortality including the following: by year of study (before or after 2005), study sample size (large versus small based on median split of included studies), study quality (Newcastle-Ottawa score ≥6 [high quality] versus <6 [low

quality]), diagnostic methodology (molecular diagnostics versus antigen and/or culture methods), disease severity (high [APACHE II ≥22, SOFA ≥5, or SAPS II ≥33] versus low), and in a subgroup of patients requiring mechanical ventilation. Publication bias was assessed by visualization of funnel plots. All analyses were performed using Review Manager (RevMan), version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

RESULTS

Our search strategy yielded 1945 original titles and abstracts after removal of duplicates. Fifty-two full-text articles were reviewed for eligibility; 21 studies [6, 7, 9–15, 19, 20, 22, 25–33] and 1 abstract [34] with a total of 2199 patients were included in our meta-analysis (Supplementary Appendix 3). A summary of studies reviewed in full text, but not fulfilling eligibility, is shown in Supplementary Appendix 4.

Table 1 and Supplementary Appendix 5 present the main characteristics of our included studies. Patient populations by study were quite variable; 3 studies included only surgical patients [6, 9, 22], 5 included patients with sepsis [11, 12, 20, 25, 26], 2 included burn patients [7, 28], 6 included only mechanically ventilated patients [10, 15, 19, 29, 31, 33], 1 included acute respiratory distress syndrome (ARDS) patients [33], and 6 used various inclusion criteria [13, 14, 27, 30, 32, 34]. Studies published after 2006 were more likely to examine specific patient populations compared with earlier studies.

Eleven studies included only CMV (immunoglobulin G) seropositive patients [7, 11, 14, 15, 20, 26, 28–30, 32, 33]. No randomized control trials met eligibility. Seventeen studies were observational [6, 7, 9–11, 14, 15, 19, 20, 22, 25, 26, 28, 30–33] and 5 were case controls [12, 13, 27, 29, 34]. Eleven studies used NAT (namely, polymerase chain reaction [PCR] testing) alone [7, 15, 20, 22, 27, 28, 30–34], whereas 5 used more than 1 method for CMV detection [10, 11, 14, 19, 25]. We included all types of ICU patients (ie, medical, general surgical, cardiac surgical, and burns). Unfortunately, few clinical characteristics, such as comorbid diseases or illness severity scoring, were reported (Table 2). The prevalence of CMV reactivation ranged from 9% to 71% (Supplementary Table 3). Supplementary Appendices 6 and 7 present our quality assessment of the included studies.

Mortality

In our primary analysis, CMV reactivation was associated with a 2.5-fold increase in ICU mortality with low heterogeneity (10 studies, n = 970 patients, OR = 2.55, 95% CI = 1.87–3.47; $P < .001$, $I^2 = 0\%$) (Figure 1). Subgroup analyses yielded similar results (Figure 2). All studies were high quality (Ottawa-Newcastle scale ≥6) so we could not stratify by study quality. Visual assessment of funnel plots did not show evidence of publication bias (Supplementary Appendix 8).

Table 1. Included Studies

Study	Design	Patient Population	Method of CMV Detection
Domart et al [6]	Observational prospective	Post-op cardiac surgery	Culture
Cook et al [12]	Case control	Sepsis	Culture
Kutza et al [25]	Observational prospective	Sepsis	PCR or pp65
Heininger et al [11]	Observational prospective	Sepsis	PCR or Culture
Cook et al [9]	Observational prospective	Postsurgical	Culture
Jaber et al [13]	Case control	General ICU	pp65
Muller et al [26]	Observational prospective	Septic shock	pp65
Limaye et al [7]	Observational prospective	Burns with TBSA >40%	PCR
Ziemann et al [27]	Case control	General ICU >14 days	PCR
Chiche et al [10]	Observational prospective	Mechanical ventilation	pp65 or culture or biopsy
Bordes et al [28]	Observational prospective	Burns with TBSA >15%	PCR
Heininger et al [14]	Observational prospective	SAPS >41, CMV IgG$^+$	PCR or culture
Chiche et al [29]	Case control	ICU admission, CMV IgG$^+$, mechanical ventilation	pp65
Coisel et al [19]	Observational prospective	Mechanical ventilation, suspected pneumonia	PCR or pp65
Al-Musawi 2014[a] [34]	Case control	Thrombocytopenia	PCR
Bravo et al [30]	Observational prospective	ICU >5 days, CMV IgG$^+$	PCR
Osman et al [31]	Observational prospective	Mechanical ventilation	PCR
Walton et al [20]	Observational prospective	General ICU	PCR
Frantzeskaki et al [15]	Observational prospective	Mechanical ventilation, CMV IgG$^+$	PCR
Lopez Roa et al [22]	Observational prospective	Post-op cardiac surgery, ICU >72 hours	PCR
Ong 2016 [33]	Observational prospective	ARDS, mechanical ventilation >96 hours, CMV IgG$^+$	PCR
Osawa 2016 [32]	Observational prospective	BSI	PCR

Abbreviations: ARDS, acute respiratory distress syndrome; BSI, bloodstream infection; CMV, cytomegalovirus; ICU, intensive care unit; Ig, immunoglobulin; op, operative; PCR, polymerase chain reaction; SAPS, simplified acute physiology score; TBSA, total body surface area.

[a]Abstract only.

Table 2. Clinical Characteristics of Included Study Populations

	CMV Reactivation								No CMV Reactivation						
Study	Number	Age	% Male	APACHE II	SOFA	SAPS II	% CMV IgG$^+$	Prevalence of CMV Reactivation %	Number	Age	% Male	APACHE II	SOFA	SAPS II	% CMV IgG$^+$
Domart et al [6]	29	59	69	15 (8)[b]	n/a	n/a	36	25	86	56	12	14 (7)[b]	n/a	n/a	25
Cook et al (1)[d] [12]	20	63	60	13 (1)[b]	n/a	n/a	n/a	10	122	58	n/a	14 (1)[b]	n/a	n/a	n/a
Kutza et al [25]	11	58	100	n/a	n/a	n/a	n/a	32	23	58	70	n/a	n/a	n/a	n/a
Heininger et al (1)[d] [11]	20	69	55	n/a	n/a	42 (9)[b]	100	36	36	67	66	n/a	n/a	42 (16)[a]	100
Cook et al (2)[e] [9]	10	69	n/a	13 (n/a)	n/a	n/a	100	9	94	58	n/a	13 (n/a)	n/a	n/a	70
Jaber et al [13]	40	62	68	n/a	n/a	51 (16)[b]	n/a	51	40	61	70	n/a	n/a	49 (16)[a]	n/a
Muller et al [26]	8	66	63	n/a	10 (7–13)[a]	n/a	100	32	17	60	59	n/a	10 (7–16)[a]	n/a	100
Limaye et al [7]	39	n/a	n/a	n/a	n/a	n/a	100	33	81	n/a	n/a	n/a	n/a	n/a	100
Ziemann et al [27]	35	68	66	n/a	n/a	n/a	65	35	64	65	67	n/a	n/a	n/a	28
Chiche et al (1)[d] [10]	39	68	69	n/a	8 (7–11)[a]	49 (16)[b]	90	19	203	62	65	n/a	9 (6–11)[a]	48 (17)[b]	72
Bordes et al [28]	15	63	n/a	n/a	n/a	n/a	100	71	6	49	n/a	n/a	n/a	n/a	100
Heininger et al (2)[e] [14]	35	68	77	n/a	8 (6–10)[a]	43 (33–47)[a]	100	41	51	69	78	n/a	9 (7–12)[a]	44 (37–53)[a]	100
Chiche et al (2)[e] [29]	15	67	60	n/a	10 (6–11)[a]	49 (30–73)[a]	100	50	15	72	60	n/a	8 (4–9)[a]	47 (36–62)[a]	100
Coisel et al [19]	21	69	64	n/a	7 (5–9)[a]	40 (31–53)[a]	95	34	40	59	60	n/a	8 (6–10)[a]	44 (31–55)[a]	76
Al-Musawi [34][f]	n/a	52	77	n/a	27 (14–48)[a]	n/a	62	52	n/a	47	66	n/a	21 (2–34)[a]	n/a	55
Bravo et al [30]	36	67	66	22.5 (11–34)[a]	n/a	n/a	100	46	42	67	74	19 (10–39) [a]	n/a	n/a	100
Osman et al [31]	35	n/a	n/a	n/a	n/a	n/a	n/a	69	16	n/a	n/a	n/a	n/a	n/a	n/a
Walton et al [20]	86	n/a	n/a	n/a	n/a	n/a	100	24	270	n/a	n/a	n/a	n/a	n/a	100
Frantzeskaki et al [15]	11	60	73	20 (4–27)[a]	10 (5)[b]	n/a	100	14	69	62	62	20 (11–43)[a]	8 (3)[b]	n/a	100
Lopez Roa et al [22]	16	n/a	n/a	n/a	n/a	n/a	100	33	32	n/a	n/a	n/a	n/a	n/a	n/a
Ong et al [33]	74	64	59	91 (71–113)[a,c]	n/a	n/a	100	27	197	64	61	76 (62–99)[a,c]	n/a	n/a	100
Osawa et al [32]	20	67	60	28 (24–31)[a]	n/a	n/a	100	20	80	61	72	24 (19–28)[a]	n/a	n/a	100

Abbreviations: APACHE, acute physiology and chronic health evaluation; CMV, cytomegalovirus; Ig, immunoglobulin; IQR, interquartile range; n/a, nonapplicable; SAPS, simplified acute physiology score; SD, standard deviation; SOFA, sequential organ failure assessment.

[a]Median (IQR).

[b]Mean (SD).

[c]APACHE IV score used.

[d]Designed the oldest of the two articles from this author included in the systematic review.

[e]Designed the most recent of the two articles from this author included in the systematic review.

[f]This reference is an abstract.

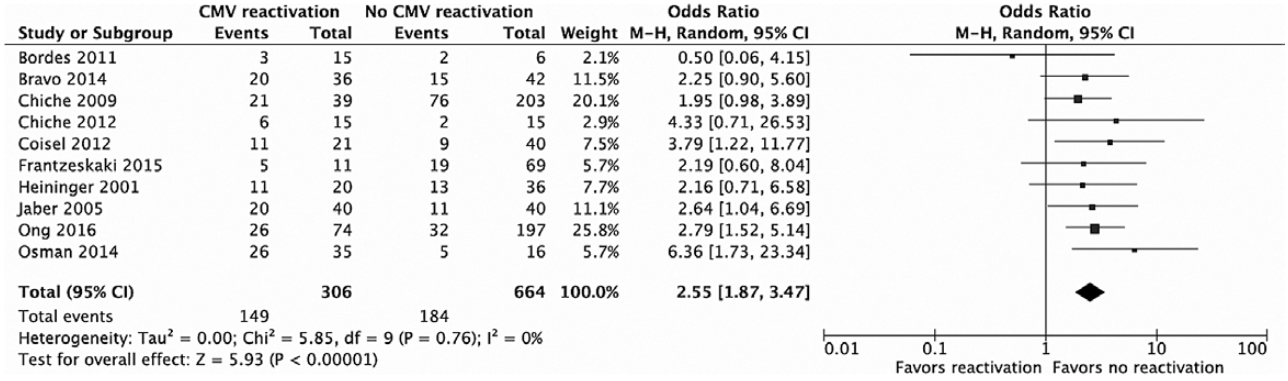

Figure 1. Association between cytomegalovirus (CMV) reactivation and intensive care unit mortality. Abbreviation: CI, confidence interval.

Secondary Outcomes

Patient-Related Outcomes.

Cytomegalovirus reactivation was associated with increased overall mortality (14 studies, n = 1814 patients, OR = 2.02, 95% CI = 1.60–2.56; P < .001, I2 = 8%) (Figure 3). Subgroup analyses yielded similar results (Supplementary Appendix 9). Again, stratification by study quality was not possible because all studies were graded as high quality.

Cytomegalovirus reactivation was also associated with increased duration of mechanical ventilation (7 studies, n = 683 patients, mean difference 6.60 days, 95% CI = 3.09–10.12; $P = .0002$, $I^2 = 79\%$) (Figure 4A). Only 7 studies [13, 19, 27, 28, 31–33] could be included because other studies were lacking any data on mechanical ventilation [6, 7, 11, 12, 15, 20, 22, 25, 30, 34] or could not be obtained despite contacting the authors [9, 10, 14, 26, 29]. Of note, the 5 studies reporting data on ventilation but missing means and/or standard deviations all demonstrated statistically significant longer durations of mechanical ventilation in patients with CMV reactivation (Cook et al [9] mean 33 vs 13 days, Chiche et al [10] median 27 vs 10 days, Heininger et al [14] median 22 vs 8 days, von Müller et al [26] median 39 vs 16 days, and Chiche et al [29] median 24 vs 8 days, in patients with and without CMV reactivation, respectively).

Finally, CMV reactivation was associated with an increase in incidence of nosocomial infections (7 studies, n = 659 patients, OR = 3.20, 95% CI = 2.05–4.98; $P < .001$, $I^2 = 0\%$) (Figure 4B) and need for RRT (3 studies, n = 343 patients, OR = 2.37, 95% CI = 1.31–4.31; $P = .005$, $I^2 = 0\%$) (Figure 4C). The most common nosocomial infections were ventilator-acquired pneumonia, bacteremia, and fungal infections.

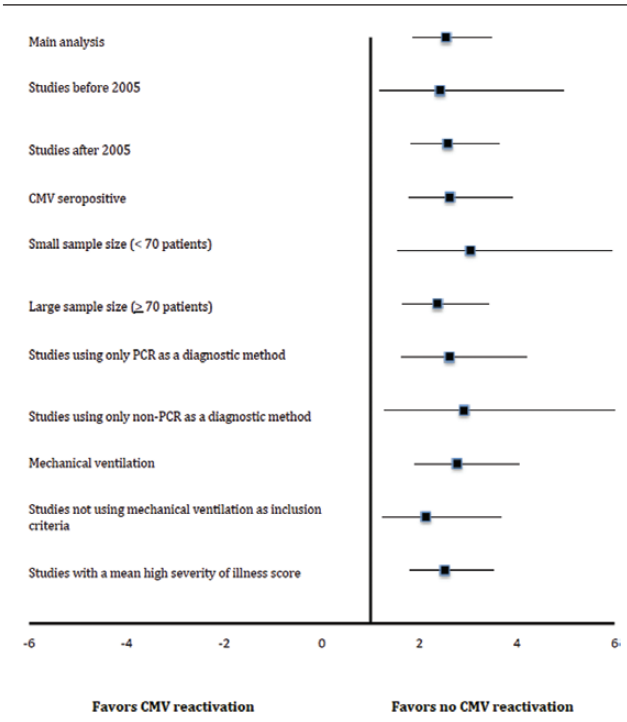

Figure 2. Subgroup analyses for intensive care unitICU mortality

Health Resource Utilization

Intensive care unit LOS was increased in patients with CMV reactivation (9 studies, n = 973 patients, mean difference 8.18 days, 95% CI = 6.14–10.22; $P < .001$, $I^2 = 65\%$) (Figure 4D). Again, 7 studies [9–11, 14, 26, 29, 33] were missing appropriate data for pooling but reported statistically significant longer LOS in patients with CMV reactivation compared with those without reactivation (Cook et al [9] mean 41 vs 19 days, Chiche et al [10] median 27 vs 10 days, Heininger et al [14] median 30 vs 12, von Müller et al [26] median 42 vs 18 days, Chiche et al [29] median 28 vs 14 days, and Heininger et al [11] text only).

Hospital LOS was not different between those with and without CMV reactivation (4 studies, n = 343 patients, mean difference 5.21 days, 95% CI = −16.68–27.11; $P = .6$, $I^2 = 91\%$) but demonstrated substantial heterogeneity. Additional data that could not be pooled, however, reported statistically significant longer hospital LOS (Cook et al [9] mean 55 vs 32 days and Heininger et al [14] median 33 vs 16 days) in patients with CMV reactivation compared with those without reactivation.

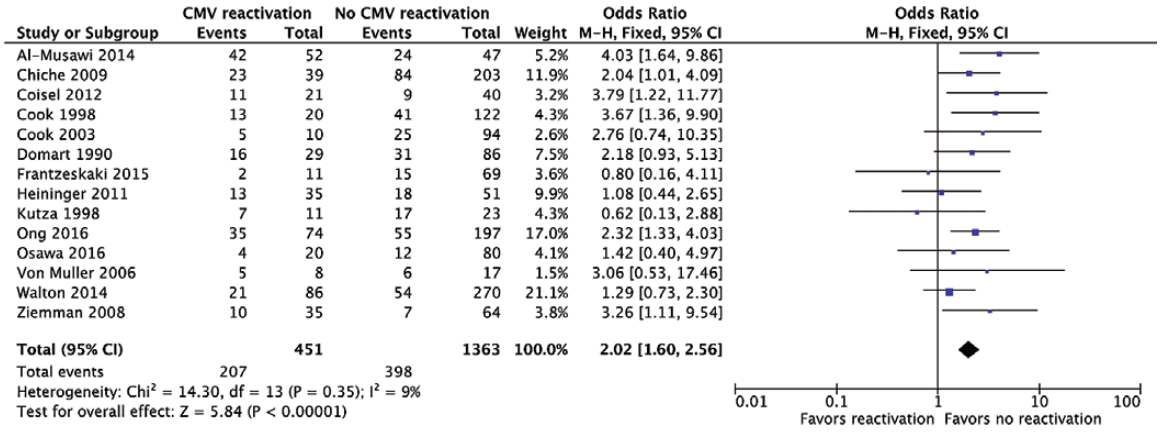

Figure 3. Association between cytomegalovirus (CMV) reactivation and overall mortality in immunocompetent critically ill patients. Abbreviation: PCR, polymerase chain reaction.

DISCUSSION

This systematic review and meta-analysis of 22 studies demonstrates an association between CMV reactivation and ICU mortality, overall mortality, duration of mechanical ventilation, incidence of nosocomial infection, need for RRT, and ICU LOS in immunocompetent critically ill patients. To our knowledge, this is the first meta-analysis demonstrating an association not only between CMV reactivation and mortality, but also morbidity and health resource use. It is also the largest meta-analysis on this subject to date.

How CMV might alter patient prognosis in critical illness, however, still remains unclear. Some argue that CMV is a primary pathogen, whereas others believe it is simply a surrogate of disease severity—a bystander in the setting of critical illness. A number of hypotheses have been suggested to explain how CMV reactivation can be pathogenic. In addition to having direct cytopathic effect [35], CMV infection can lead to the generation of inflammatory mediators, perpetuating the harmful proinflammatory/anti-inflammatory imbalance seen in critical illness [36]. It has also been proposed that CMV has immunosuppressive effects—via its interference with antigen processing and impaired T-cell proliferation [37–39].

Some authors have raised the possibility that CMV reactivation may simply be a marker of more severe illness [40]. For example, patients with septic shock can develop a state of immunoparalysis, also called compensatory anti-inflammatory response syndrome [31], that may increase the risk of CMV reactivation. Some have also suggested that immunoparalysis may be implicated in the increased risk of CMV reactivation associated with blood transfusion [7, 41], a phenomenon that often occurs in ICU. Moreover, bacterial infection may result in the release of endotoxin and tumor necrosis factor, which may also promote reactivation of latent CMV infection [31]. Finally, infusion of exogenous catecholamines has been shown to encourage CMV reactivation [31].

However, despite lacking data for pooling in many studies, our sensitivity analyses in patients with high versus low illness severity scores demonstrated similar associations between CMV and mortality. We do recognize that our analyses were subject to substantial heterogeneity given that we stratified using various severity scoring systems (APACHE II, SOFA, and SAPS II scores). Of interest, in studies that examined the interaction between CMV reactivation and severity of illness in adjusted analyses, severity of illness was not an independent predictor of CMV reactivation [9–11, 13, 15, 32]. In addition, in studies adjusting for severity of illness, CMV reactivation and mortality remained independently associated. Finally, some would argue that our included studies may suffer from time-dependent bias. Although such bias cannot be ruled out, it seems unlikely because CMV reactivation occurred relatively early in all studies.

Therefore, although the evidence is limited, the available data and plausible mechanisms described above suggest that CMV reactivation may be associated with higher mortality, and not simply correlated with disease severity. Further studies, specifically designed to test the associations between disease severity, CMV reactivation, and mortality in immunocompetent critically ill patients, are sorely needed.

The impact of CMV prophylaxis or preemptive therapy on outcomes in CMV- seropositive ICU patients remains to be determined. Epidemiological data have suggested a potential benefit [42]. Randomized control trials are currently ongoing [48, 49]. The GRAIL (Study of Ganciclovir/Valganciclovir for Prevention of Cytomegalovirus Reactivation in Acute Injury of the Lung and Respiratory Failure) study plans to examine the effect of antiviral prophylaxis on serum interleukin (IL)-6 levels, CMV reactivation, and mortality in immunocompetent mechanically ventilated ICU patients [43]. The PTH (Preemptive Treatment for Herpesviridae) study will specifically examine the effect of preemptive treatment in ICU patients requiring prolonged mechanical ventilation (>96 hours) [49]. Outcomes will include

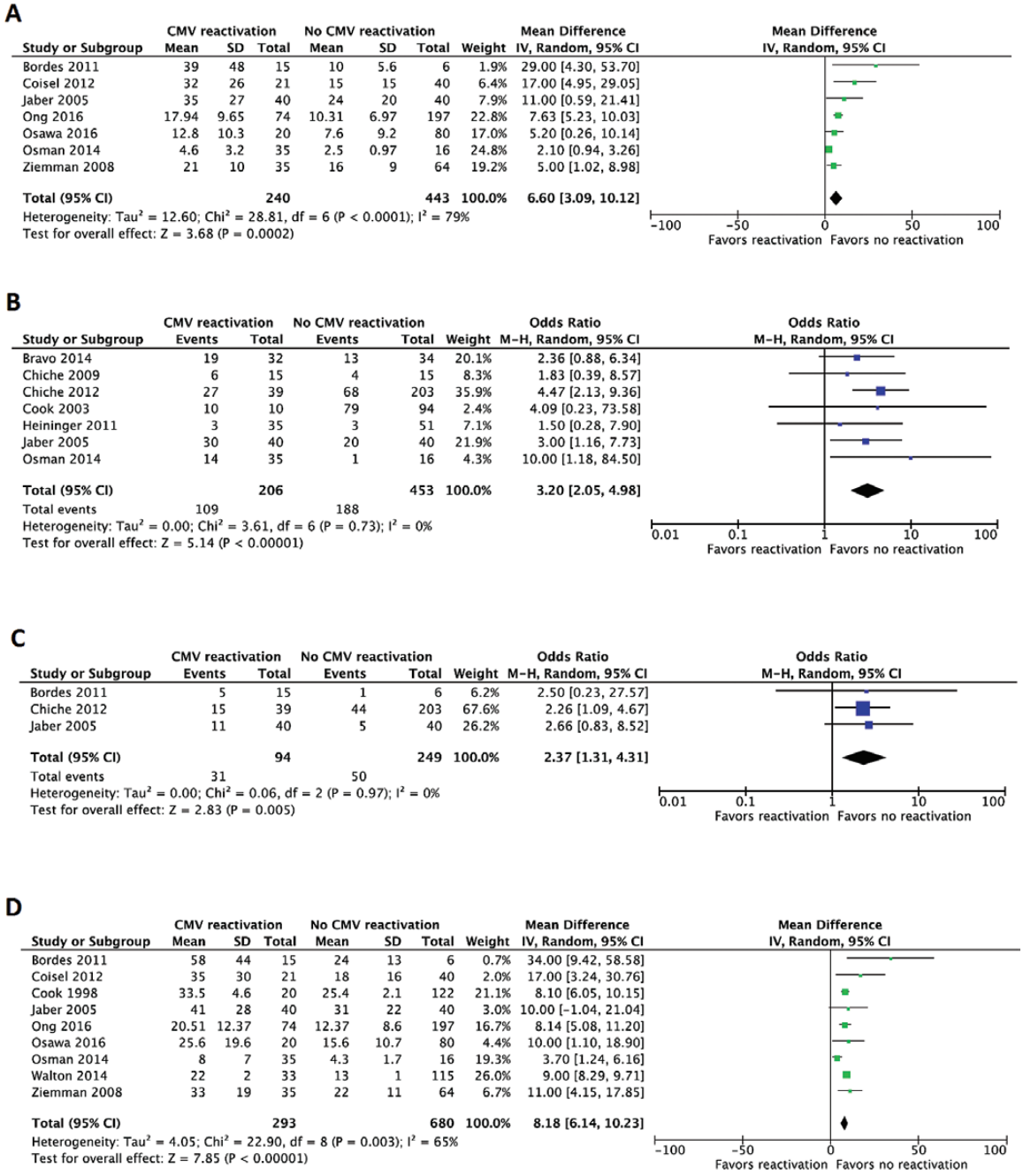

Figure 4. (A) Association between cytomegalovirus (CMV) reactivation and mechanical ventilation duration in immunocompetent critically ill patients. (B) Association between CMV reactivation and nosocomial infection in immunocompetent critically ill patients. (C) Association between CMV reactivation and need for renal replacement therapy in immunocompetent critically ill patients. (D) Association between CMV reactivation and intensive care unit length of stay in immunocompetent critically ill patients. Abbreviations: CI, confidence interval; SD, standard deviation.

ventilator-free days, mortality, and a number of other clinical outcomes [44]. We hope these important studies will provide some much needed answers in the near future.

How CMV reactivation may result in longer durations of ventilation is also somewhat unclear. Evidence suggests the lungs may play an important role in the pathogenicity of CMV—as a major site of CMV latency [45] and reactivation [9, 12]. Once reactivated, CMV infection can result in the release of pulmonary IL-11 [46], secretion of fibrogenic cytokines, and the development of ARDS [47, 48]. This could potentially explain the longer duration of mechanical ventilation, as well as higher incidence of nosocomial pulmonary infection and longer lengths of stay, observed in patients with CMV reactivation in this systematic review.

The association between CMV reactivation and need for RRT is also of interest. To the best of our knowledge, it has never

been reported. This association could be explained by the proinflammatory effect of CMV infection [36]. Indeed, inflammatory cytokines have been implicated in the pathogenesis of sepsis-induced acute kidney injury [49]. However, this hypothesis will have to be explored in further studies.

In terms of limitations, we found significant inconsistencies in data reporting across studies as shown in Table 2. For example, illness severity was inconsistently reported and, when available, was reported using a variety of severity scores, making it difficult to pool data. In addition, despite good quality reporting, only observational studies could be included because no randomized trials met eligibility. Therefore, our results are prone to bias and confounding based on study type alone.

Only few studies reported risk-adjusted outcomes, and, of those that did, most did not take into account important characteristics such as premorbid disease. Therefore, the risk of residual confounding in our analysis remains high. Few studies provided enough clinical characteristics of their study populations to perform meta-regression. In addition, attributable mortality was reported in only 1 study.

Some of our analyses demonstrated high heterogeneity likely due to the evolution of ICU care over time, different methods of CMV detection, the variability in performance of PCR assays, frequency of testing, and varied study populations. We did attempt to address this by conducting numerous sensitivity analyses. However, some studies reported data that was inappropriate for pooling. Of note, studies missing appropriate duration of mechanical ventilation or LOS data (means and standard deviations) reported similar outcomes as in our meta-analyses. Therefore, inclusion of these studies would have narrowed our CIs but would not have changed our final conclusions, with the exception of hospital LOS—where additional data might have resulted in statistical significance.

We also examined gray literature, which can be considered both a weakness (because this is not peer-reviewed data) and a strength (because it allowed us to reduce publication bias). Finally, one must consider that the distinction between CMV primary infection, reactivation, and disease is difficult without prior serostatus and/or tissue biopsy. Although CMV primary infection in ICU would be rare, as would CMV disease in immunocompetent patients, the possibility of misclassification bias cannot be excluded.

CONCLUSIONS

In conclusion, in this systematic review and meta-analysis, CMV reactivation was associated with increased ICU and overall mortality, prolonged mechanical ventilation, higher incidence of nosocomial infection, increased need for RRT, and prolonged ICU stay in immunocompetent critically ill patients. This evidence, despite various limitations, suggests that CMV reactivation may not simply be a marker of disease severity but may have a true pathogenic effect. In addition, the impact of CMV prophylaxis and/or preemptive therapy on outcomes in immunocompetent critically ill patients remains to be determined.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. P. L. and W. I. S. conceived the study question and design. P. L. and W. I. S. drafted the manuscript; R. F. created the search strategy; P. L. and J. C. selected studies and extracted data; P. L. performed statistical analysis; W. I. S. is the guarantor of the review and takes responsibility for the integrity of the data and the accuracy of the analysis. All authors had full access to the data (including statistical reports and tables) in the study and approved the final manuscript.

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References

1. Krech U. Complement-fixing antibodies against cytomegalovirus in different parts of the world. Bull World Health Organ **1973**; 49:103–6.
2. Cannon MJ, Schmid DS, Hyde TB. Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. Rev Med Virol **2010**; 20:202–13.
3. Kondo K, Kaneshima H, Mocarski ES. Human cytomegalovirus latent infection of granulocyte-macrophage progenitors. Proc Natl Acad Sci U S A **1994**; 91:11879–83.
4. Papazian L, Hraiech S, Lehingue S, et al. Cytomegalovirus reactivation in ICU patients. Intensive Care Med **2016**; 42:28–37.
5. Requião-Moura LR, deMatos AC, Pacheco-Silva A. Cytomegalovirus infection in renal transplantation: clinical aspects, management and the perspectives. Einstein (Sao Paulo) **2015**; 13:142–8.
6. Domart Y, Trouillet JL, Fagon JY, et al. Incidence and morbidity of cytomegaloviral infection in patients with mediastinitis following cardiac surgery. Chest **1990**; 97:18–22.
7. Limaye AP, Kirby KA, Rubenfeld GD, et al. Cytomegalovirus reactivation in critically ill immunocompetent patients. JAMA **2008**; 300:413–22.
8. Lopez Roa P, Perez-Granda MJ, Munoz P, et al. A prospective monitoring study of cytomegalovirus infection in non-immunosuppressed critical heart surgery patients. PLoS One **2015**; 10:e0129447.
9. Cook CH, Martin LC, Yenchar JK, et al. Occult herpes family viral infections are endemic in critically ill surgical patients. Crit Care Med **2003**; 31:1923–9.
10. Chiche L, Forel JM, Roch A, et al. Active cytomegalovirus infection is common in mechanically ventilated medical intensive care unit patients. Crit Care Med **2009**; 37:1850–7.
11. Heininger A, Jahn G, Engel C, et al. Human cytomegalovirus infections in nonimmunosuppressed critically ill patients. Crit Care Med **2001**; 29:541–7.
12. Cook CH, Yenchar JK, Kraner TO, et al. Occult herpes family viruses may increase mortality in critically ill surgical patients. Am J Surg **1998**; 176:357–60.
13. Jaber S, Chanques G, Borry J, et al. Cytomegalovirus infection in critically ill patients: associated factors and consequences. Chest **2005**; 127:233–41.
14. Heininger A, Haeberle H, Fischer I, et al. Cytomegalovirus reactivation and associated outcome of critically ill patients with severe sepsis. Crit Care **2011**; 15:R77.
15. Frantzeskaki FG, Karampi ES, Kottaridi C, et al. Cytomegalovirus reactivation in a general, nonimmunosuppressed intensive care unit population: incidence, risk factors, associations with organ dysfunction, and inflammatory biomarkers. J Crit Care **2015**; 30:276–81.
16. Osawa R, Singh N. Cytomegalovirus infection in critically ill patients: a systematic review. Crit Care **2009**; 13:R68.
17. Kalil AC, Florescu DF. Prevalence and mortality associated with cytomegalovirus infection in nonimmunosuppressed patients in the intensive care unit. Crit Care Med **2009**; 37:2350–8.

18. Kalil AC, Florescu DF. Is cytomegalovirus reactivation increasing the mortality of patients with severe sepsis? Crit Care **2011**; 15:138.
19. Coisel Y, Bousbia S, Forel JM, et al. Cytomegalovirus and herpes simplex virus effect on the prognosis of mechanically ventilated patients suspected to have ventilator-associated pneumonia. PLoS One **2012**; 7:e51340.
20. Walton AH, Muenzer JT, Rasche D, et al. Reactivation of multiple viruses in patients with sepsis. PLoS One **2014**; 9:e98819.
21. Ong DS, Klein Klouwenberg PM, Verduyn Lunel FM, et al. Cytomegalovirus seroprevalence as a risk factor for poor outcome in acute respiratory distress syndrome*. Crit Care Med **2015**; 43:394–400.
22. Lopez Roa P, Hill JA, Kirby KA, et al. Coreactivation of human herpesvirus 6 and cytomegalovirus is associated with worse clinical outcome in critically Ill adults. Crit Care Med **2015**; 43:1415–22.
23. Lachance P, Chen J, Featherstone R, Sligl W. Impact of cytomegalovirus reactivation on clinical outcomes in immunocompetent critically ill patients: protocol for a systematic review and meta-analysis. Syst Rev **2016**; 5:127.
24. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 12 December 2015.
25. Kutza AS, Muhl E, Hackstein H, et al. High incidence of active cytomegalovirus infection among septic patients. Clin Infect Dis **1998**; 26:1076–82.
26. von Müller L, Klemm A, Weiss M, et al. Active cytomegalovirus infection in patients with septic shock. Emerg Infect Dis **2006**; 12:1517–22.
27. Ziemann M, Sedemund-Adib B, Reiland P, et al. Increased mortality in long-term intensive care patients with active cytomegalovirus infection. Crit Care Med **2008**; 36:3145–50.
28. Bordes J, Maslin J, Prunet B, et al. Cytomegalovirus infection in severe burn patients monitoring by real-time polymerase chain reaction: a prospective study. Burns **2011**; 37:434–9.
29. Chiche L, Forel JM, Thomas G, et al. Interferon-γ production by natural killer cells and cytomegalovirus in critically ill patients. Crit Care Med **2012**; 40:3162–9.
30. Bravo D, Clari MA, Aguilar G, et al. Looking for biological factors to predict the risk of active cytomegalovirus infection in non-immunosuppressed critically ill patients. J Med Virol **2014**; 86:827–33.
31. Osman NM, Sayed NM, Abdel-Rahman SM, et al. The impact of cytomegalovirus infection on mechanically ventilated patients in the respiratory and geriatric intensive care units. Egyptian Journal of Chest Diseases and Tuberculosis **2014**; 63:239–45.
32. Osawa R, Wagener M, Singh N. Cytomegalovirus infection in patients with sepsis due to bloodstream infections: lower risk and better outcomes in new versus already hospitalised intensive care unit admissions. Anaesth Intensive Care **2016**; 44:571–80.
33. Ong DS, Spitoni C, Klein Klouwenberg PM, et al. Cytomegalovirus reactivation and mortality in patients with acute respiratory distress syndrome. Intensive Care Med **2016**; 42:333–41.
34. Al Musawi T, Khawaldeh A, Gonheim D, et al. Cytomegalovirus (CMV) in non-immunocompromised critically Ill patients. **2014:** P0470. Available at: www.escmid.org/escmid_publications.
35. Poncet D, Pauleau AL, Szabadkai G, et al. Cytopathic effects of the cytomegalovirus-encoded apoptosis inhibitory protein vMIA. J Cell Biol **2006**; 174:985–96.
36. Grundy JE. Virologic and pathogenetic aspects of cytomegalovirus infection. Rev Infect Dis **1990**; 12 (Suppl 7):S711–9.
37. Barry SM, Johnson MA, Janossy G. Cytopathology or immunopathology? The puzzle of cytomegalovirus pneumonitis revisited. Bone Marrow Transplant **2000**; 26:591–7.
38. Filteau S, Rowland-Jones S. Cytomegalovirus infection may contribute to the reduced immune function, growth, development, and health of HIV-exposed, uninfected African children. Front Immunol **2016**; 7:257.
39. Wikby A, Johansson B, Olsson J, et al. Expansions of peripheral blood CD8 T-lymphocyte subpopulations and an association with cytomegalovirus seropositivity in the elderly: the Swedish NONA immune study. Exp Gerontol **2002**; 37:445–53.
40. Cook CH. Cytomegalovirus reactivation in "immunocompetent" patients: a call for scientific prophylaxis. J Infect Dis **2007**; 196:1273–5.
41. Al-Omari A, Aljamaan F, Alhazzani W, et al. Cytomegalovirus infection in immunocompetent critically ill adults: literature review. Ann Intensive Care **2016**; 6:110.
42. Millar J, Park SC, Cowley N, et al. Anti-viral prophylaxis for prevention of cytomegalovirus (CMV) reactivation in immunocompetent patients in critical care. Intensive Care Med **2013**: S311. doi:10.1007/s00134-013-3095-5.
43. Boeckh M. Study of Ganciclovir/Valganciclovir for Prevention of Cytomegalovirus Reactivation in Acute Injury of the Lung and Respiratory Failure (GRAIL). Available at: https://clinicaltrials.gov/ct2/show/NCT01335932. Accessed 16 May 2016.
44. Papazian L. Preemptive Treatment for Herpesviridae. Available at: https://clinicaltrials.gov/ct2/show/NCT02152358. Accessed 1 October 2016.
45. Balthesen M, Messerle M, Reddehase MJ. Lungs are a major organ site of cytomegalovirus latency and recurrence. J Virol **1993**; 67:5360–6.
46. Blanquer J, Chilet M, Benet I, et al. Immunological insights into the pathogenesis of active CMV infection in non-immunosuppressed critically ill patients. J Med Virol **2011**; 83:1966–71.
47. Navarro D. Expanding role of cytomegalovirus as a human pathogen. J Med Virol **2016**; 88:1103–12.
48. Cook CH, Zhang Y, Sedmak DD, et al. Pulmonary cytomegalovirus reactivation causes pathology in immunocompetent mice. Crit Care Med **2006**; 34:842–9.
49. Schrier RW, Wang W. Acute renal failure and sepsis. N Engl J Med **2004**; 351:159–69.