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SYSTEMATIC REVIEW

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Diastolic dysfunction and mortality in septic patients: a systematic review and meta-analysis

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Abstract *Background:* Myocardial dysfunction may contribute to the haemodynamic instability which accompanies sepsis, and may result in circulatory failure. There is no association between systolic dysfunction (SD) and mortality in septic patients and there is conflicting evidence regarding the effects of diastolic dysfunction (DD) on mortality in septic patients. *Methods:* We conducted a systematic review and meta-analysis to investigate DD and mortality in septic patients. We included studies conducted in this patient population which investigated the association between DD reported according to tissue Doppler imaging (TDI) criteria and mortality, using the longest reported follow-up. As a secondary endpoint, we evaluated the association between SD and mortality according to the results reported by the retrieved studies. *Results:* We included seven studies in our meta-analysis with 636 septic patients, 48 % of them were found to have DD. We found a significant association between DD and mortality (RR 1.82, 95 % CI 1.12–2.97, $p = 0.02$). This finding remained valid in a further analysis which including an older study reporting DD without TDI criteria. Five studies reported data on SD for a total of 581 patients, 29.6 % of them with SD. No association was found between SD and mortality (RR 0.93, 95 % CI 0.62–1.39, $p = 0.73$). Looking at subgroups, there was a trend towards higher mortality comparing isolated DD or combined SD–DD vs normal heart function ($p = 0.10$ and $p = 0.05$, respectively). *Conclusions:* Diastolic dysfunction is common in septic patients and it is associated with mortality. Systolic dysfunction is less common and is not associated with mortality in this group of patients.

Keywords Systolic dysfunction · Echocardiography · Intensive care · Tissue Doppler imaging · Septic shock · Severe sepsis

Introduction

The clinical syndrome of sepsis results from the individual's response to an infective process, and may be associated with profound haemodynamic disturbance [1, 2]. Sepsis still accounts for substantial mortality and morbidity with circulatory failure and consequential multi-organ failure the main mechanism [3]. Septic shock

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is characterized by profound vasodilation requiring administration of vasopressor agents to maintain organ perfusion [2]. Additionally, septic patients may exhibit pronounced myocardial dysfunction [4, 5], not only with left and/or right ventricular (LV and/or RV) systolic impairment [6] but also with reversible LV diastolic dysfunction (DD) [7].

Heart failure (HF) with preserved LV ejection fraction (EF) is often unrecognized [8]. Survival rates remain unchanged despite an increasing incidence over the past 15 years [9]. More than half of patients hospitalized with HF have preserved LV systolic function [8–10], and LV DD may account for a significant incidence of acute pulmonary oedema episodes associated with hypertension [11].

Conflicting evidence regarding the effects of DD on the mortality of septic patients exists. The two largest studies to date have displayed contradictory results. Indeed, Landesberg et al. [12] demonstrated a sixfold higher mortality in septic patients with DD, when compared with patients with normal LV function. In contrast, Pulido et al. [13] found no correlation between DD and increased mortality. The same discrepancy has been found in experimental studies where diastolic compliance was increased [14] or decreased [15].

In this systematic review and meta-analysis we set out to investigate the contribution of DD to the mortality of patients with severe sepsis and/or septic shock.

Methods

This systematic review and meta-analysis was performed in accordance with the MOOSE [16] and PRISMA guidelines [17]. The review was registered with the international prospective register of systematic reviews (PROSPERO–number CRD42014013593).

Eligibility criteria

Observational studies investigating the impact of DD on mortality of patients with sepsis, severe sepsis and/or septic shock, as defined by international consensus [18], were included if tissue Doppler imaging (TDI) was used for assessment of diastolic function. TDI parameters exhibit less preload dependency [19], and offer greater reliability in septic patients. Inclusion criteria for clinical studies were prespecified using the PICOS format (Table 1). Paediatric populations were excluded to minimise heterogeneity. Only case series reporting DD data and outcomes from at least five patients were included.

Analysis of outcomes

We chose to analyse mortality at the longest reported follow-up period, since studies reported mortality at varying time intervals. As primary endpoint, patients with DD were compared to all patients with normal diastolic function, regardless of their systolic function. We also performed a sensitivity analysis looking at the effect of DD on mortality including also studies that used other criteria than TDI for the assessment of diastolic function.

As secondary endpoints of the meta-analysis, and using only the data available from the retrieved studies, we also analysed the correlation between (1) the presence of systolic dysfunction (SD) and mortality as compared with patients with no SD; (2) presence of isolated DD, isolated SD and combined SD + DD and mortality as compared with patients with normal heart function.

Identification of studies

A systematic search of the electronic databases MEDLINE and EMBASE was performed through the NICE Healthcare Databases Advanced Search. Relevant titles were also identified by hand searching previous reviews on the topic. There was no date restriction and only articles published in English, Spanish, French, German or Italian were considered. Duplicates were filtered through automated function and then manually searched. Titles retrieved from EMBASE as conference abstracts were considered only if published after September 2011 to allow a reasonable time for adequate peer-review process. The last search update was on 21 October 2014.

The findings of two search terms groups were combined: the items “bacteraemia”, “bacteremia”, “respiratory distress syndrome”, “sepsis”, “septic shock”, “severe sepsis”, “systemic inflammatory response” were used for the first group; “diastole”, “diastolic dysfunction”, “diastolic function”, “diastolic heart failure”, “Doppler tissue index”, “E/A ratio”, “E’”, “left ventricular dysfunction”, “pulsed Doppler”, “tissue Doppler index”, “Vp” for the second group. The flow of references was managed with the Endnote X7 citation manager.

Study selection and data extraction

Two investigators (FS, CC) independently screened titles and abstracts produced by the search and identified potentially relevant articles. Full-text articles that were identified as relevant were then assessed against the eligibility criteria. Discrepancies were resolved by consensus and/or by involving other authors (NF, MC).

Table 1 PICOS approach for selecting clinical studies in the systematic search

PICOS	Characteristics of clinical studies included for the qualitative synthesis and meta-analysis
1. Participants	Adult patients with sepsis, severe sepsis and/or septic shock
2. Intervention	Echocardiographic assessment of the diastolic function within 72 h of ICU admission. Assessment performed with tissue Doppler imaging and according to currently validated guidelines (American, European, British), or data available for evaluation
3. Comparison	Primary: Patients with DD were compared to all patients with no DD Secondary: Patients with SD were compared to all patients with no SD Patients with isolated DD, isolated SD and combined SD + DD were compared to patients with normal heart function
4. Outcomes	Mortality (at longest follow-up available)
5. Study design	Prospective clinical studies. Case series only if including more than five patients

DD diastolic dysfunction, *SD* systolic dysfunction

Two reviewers (FS, CC) independently extracted data from individual studies and entered information into a pre-designed data collection form. Data extracted from each study included the number of septic patients examined, the different criteria used for identifying DD, and data on mortality (at different time intervals). If data were not available we directly contacted the corresponding author via email. In case of absent reply, we conducted an online search to identify the contacts of all the co-author's emails.

Statistical analysis

The main dichotomous outcome of mortality at the longest follow-up was analysed using a Mantel Haenzel model. Outcomes were reported as risk ratios (RR) with 95 % confidence intervals (CI). *P* values were two-tailed and considered statistically significant if less than 0.05.

The x^2 (Cochran Q) test was used to establish whether statistical heterogeneity was present. A $Q > df$ (degrees of freedom) suggested the presence of heterogeneity, which was confirmed if $p \leq 0.10$. I^2 statistic was used to measure heterogeneity and values of 0–24.9, 25–49.9, 50–74.9 and greater than 75 % were considered as none, low, moderate and high heterogeneity, respectively [20]. A random effects model was used if I^2 value was higher than 25 %. Sensitivity analysis was performed using the 'leave one out' approach in order to detect the influence of single studies on the observed effect [21]. We also performed a sensitivity analysis according to methods of assessing DD, TDI and non-TDI. Publication bias was investigated using the Egger's regression asymmetry test [22].

Meta-analysis was performed using review manager (Revman) for MAC (version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Comprehensive meta-analysis version 2.2.064 was used to perform the Egger's regression.

Results

Study selection

The literature search produced 171 titles on MEDLINE and 1,368 on EMBASE. After eliminating 70 duplicates, only 215 titles were identified as potentially relevant. Abstracts were then appraised against inclusion criteria and 23 full-text articles were retrieved for further analysis. Finally, we identified ten studies as suitable for the meta-analysis; however, only seven articles were included for quantitative analysis [12, 13, 23–27]. One study was excluded because it did not use TDI criteria for assessing DD, was published in 1997 and used the pulmonary vein flow pattern (S/D ratio) as criteria for defining DD [28]. It was not possible to contact one group of authors [29], and we could not find contact details for information regarding an abstract reporting relevant data in a recent conference (ESICM LIVES 2013) [5]. Figure 1 shows the PRISMA flow chart of the systematic search and qualitative synthesis.

Observational studies characteristics

From the qualitative analysis we selected seven observational studies [12, 13, 23–27] assessing DD with TDI criteria and including 647 patients with sepsis reported outcomes of patients with DD. Only one study used transoesophageal echocardiography [23]. In most of the selected studies, the quantification of DD was performed using criteria suggested by the American Society of Echocardiography guidelines (Supplemental Digital Content–Appendix 1) [30]. In one study of 106 patients, according to the corresponding author, among the patients classified as normal heart function, 11 were assessed for their systolic function but not with regards to DD. Therefore we excluded these 11 patients when assessing outcomes according to the presence of DD and in

subgroup analyses [13], leaving a final population of 636 patients for meta-analysis of the primary outcome.

Only three studies provided a breakdown of age according to survivors and non-survivors [12, 23, 24], and in two of them [12, 24] surviving patients were significantly younger than non-survivors (Table 2). Six of the included studies reported also rates of mechanical ventilation, ranging from 49 to 100 % of the patient population [12, 23–27]. No studies provide a breakdown of age and/or mechanical ventilation according to the diastolic function (Table 2).

Among the above studies, a total of 305 patients included in the meta-analysis were classified with any degree of DD (48 %), the reported incidence ranging from 20 to 57.1 %, and three studies reported an incidence of 50 % or higher (Table 3).

Five studies [12, 13, 23, 24, 26] also reported data on the presence of SD, with an overall incidence of 29.6 % ($n = 172/581$), varying from 23.3 to 54.2 % (Supplemental Digital Content–Appendix 2). One study reported data on SD and mortality, but was excluded since normal and mildly impaired systolic function (EF < 45 %) were included in the same group [25]. Finally, a breakdown of echocardiographic findings according to both systolic and diastolic function (normal heart function; isolated DD; isolated SD; combined SD + DD) is provided as Supplemental Digital Content (Appendix 3).

Diastolic dysfunction and mortality

In the seven studies included in the meta-analysis of primary outcome [12, 13, 23–27], mortality at longest follow-up was significantly higher in patients with DD vs patients with normal diastolic function (RR 1.82, 95 % CI 1.12–2.97, $p = 0.02$; Fig. 2a). There was significant statistical heterogeneity ($x^2p = 0.0002$, I^2 77 %). This finding was robust (RR 1.84, 95 % CI 1.19–2.83, $p = 0.0006$) to the sensitivity analysis that included also a study that used non-TDI criteria to assess DD ($x^2p = 0.0004$; I^2 73 %) [12, 13, 23–28]. In this analysis, an adjustment of the data was necessary for four young patients (<30 years old) since these patients were erroneously deemed to have DD for a S/D ratio <1, a normal finding for young patients.

Performing the 'leave one out' analysis did not change the overall direction or significance of the pooled findings. Point estimates ranged from 1.58 to 2.32. The biggest contributor to high heterogeneity was the study by Pulido et al. [13] and its removal led to lower heterogeneity (33 %).

Systolic dysfunction and mortality

Mortality data on patients with SD was reported by five studies [12, 13, 23, 24, 26] encompassing 570 patients. All the studies used a cut-off of LVEF of 50 % to identify those with SD. There was no statistically significant difference in mortality rates in patients with SD vs patients with normal systolic function (RR 0.93, 95 % CI 0.62–1.39, $p = 0.73$; Fig. 2b). Significant statistical heterogeneity was detected in this analysis ($x^2p = 0.02$, $I^2 = 68$ %). Sensitivity 'leave one out' analysis did not alter the cumulative effect estimate. No study subtraction rendered the results significant with point estimates

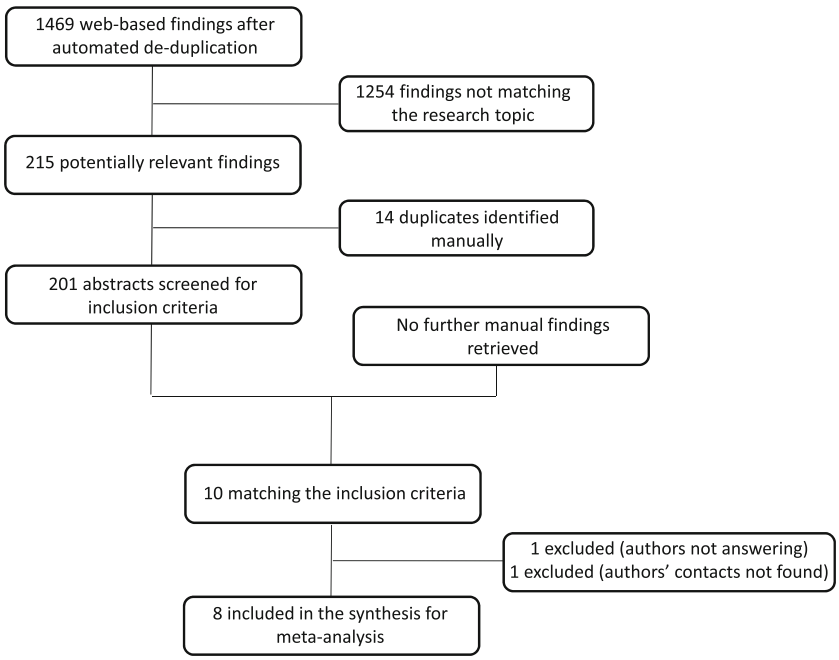

Fig. 1 Flow chart of the systematic search and of the qualitative synthesis for meta-analysis

Table 2 Characteristics of included observational studies

Author/year	Population	TTE vs TEE	Age	% MV	DD cut-off	SD cut-off	Longest follow-up
Etchecopar-Chevreuil et al. [23]	35 ICU patients with septic shock	TEE within 12 h	Alive 54 ± 18, died 68 ± 14	100 %	Lateral $e' < 8.5$ cm/s	LVEF < 50 %	28 days
Landesberg et al. [24]	106 ICU patients with severe sepsis and septic shock	TTE on admission or asap	Alive 56 ± 21, died 70 ± 17*	100 %	Septal $e' < 8$ cm/s	LVEF < 50 %	12 months
Landesberg et al. [12]	262 ICU patients with severe sepsis and septic shock	TTE asap + day after admission	Alive 60 ± 20, died 71 ± 15*	100 %	Septal $e' < 8$ cm/s	LVEF < 50 %	12 months
Mokart et al. [25]	45 ICU oncological patients with septic shock	TTE within 24 h	56 ± 13	49 %	ASE guidelines (lateral e′)	LVEF < 45 %	ICU stay
Mourad et al. [26]	72 ICU oncological patients with septic shock	TTE within 48 h[b]	58 ± 12	54 %	Lateral $e' < 8$ cm/s	LVEF < 50 %	ICU stay
Pulido et al. [13]	106[a] ICU patients with severe sepsis or septic shock	TTE within 24 h	65 ± 15	N/A	ASE guidelines (septal and lateral e′)	LVEF < 50 %	12 months
Sturgess et al. [27]	21 ICU patients with septic shock	TTE within 72 h[c]	65 ± 17	76 %	ASE guidelines (septal e′)	LVEF < 55 %	Hospital stay

The timing of echocardiographic assessment is intended from admission to intensive care unit (ICU). Age is reported as mean and standard deviation or as median and interquartile range according to the data provided

DD diastolic dysfunction, *SD* systolic dysfunction, *ASE* American Society of Echocardiography, *MV* mechanical ventilation, *TEE* transoesophageal echocardiography, *TTE* transthoracic echocardiography

* $p < 0.05$

[a] Eleven patients were not assessed with regards to DD

[b] 72 % of patients had a TTE within 24 h

[c] 71 % of patients had a TTE within 24 h

Table 3 Incidence of left ventricular diastolic dysfunction in the selected studies for the meta-analysis

	Diastolic dysfunction	Normal diastolic function	Population (*n*)
Etchecopar-Chevreuil et al. [23]	7 (20 %)	28 (80 %)	35
Landesberg et al. [24]	53 (50 %)	53 (50 %)	106
Landesberg et al. [12]	143 (54.6 %)	119 (45.4 %)	262
Mokart et al. [25]	18 (40 %)	27 (60 %)	45
Mourad et al. [26]	33 (45.8 %)	39 (54.2 %)	72
Pulido et al. [13]	39 (36.8 %)	56 (63.2 %)[a]	95
Sturgess et al. [27]	12 (57.1 %)	9 (42.9 %)	21
Totals	305 (48 %)	331 (52 %)	636

[a] Eleven patients in this study were classified as normal heart function but they had no assessment of diastolic function and were excluded in our analysis

ranging from 0.73 to 1.21. The study by Mourad et al. [26] was the biggest contributor to high between-study heterogeneity and by excluding this study, heterogeneity was reduced to 40 %.

Subgroups of systolic and diastolic function and mortality

We also compared three subgroups of LV dysfunction (isolated DD; isolated SD; combined SD + DD) with normal LV function: we found a trend towards significantly higher mortality risk only for combined SD + DD (RR 2.06, 95 % CI 1.00–4.27, $p = 0.05$, $x^2p = 0.001$, $I^2 = 78$ %) and isolated DD (RR 2.02, 95 % CI 0.87–4.69, $p = 0.10$, $x^2p < 0.0001$, $I^2 = 87$ %). Isolated SD was not associated with mortality when compared to normal LV function (RR 1.11, 95 % CI 0.66–1.89, $p = 0.69$, $x^2p = 0.14$, $I^2 = 43$ %). A summary of the findings of the quantitative analyses is provided in Table 4.

Publication bias

The presence of publication bias was assessed using the Egger's regression test. We found no statistically significant evidence of publication bias for both mortality analyses, DD vs no DD ($p = 0.34$) and SD vs no SD ($p = 0.185$).

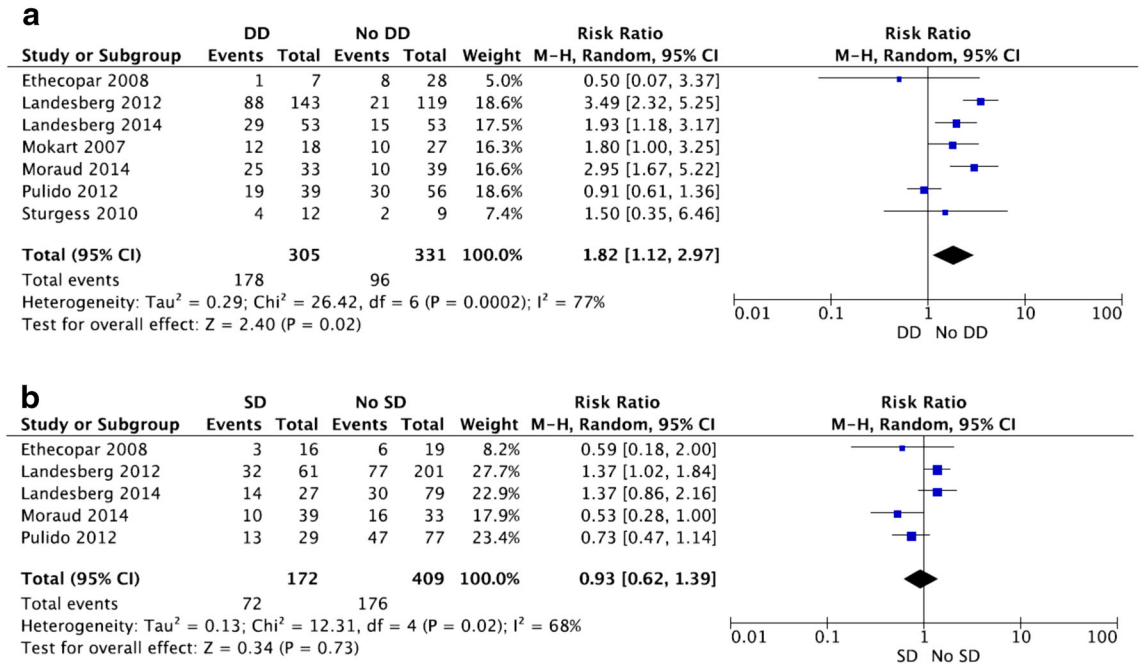

Fig. 2 **a** Effect of diastolic dysfunction vs no diastolic dysfunction on mortality at longest follow-up in septic patients. **b** Effect of systolic dysfunction vs no systolic dysfunction on mortality at longest follow-up in septic patients

Discussion

Our meta-analysis included seven studies providing mortality data in a population of 636 septic patients according to echocardiographic assessment of their diastolic function. We found an association between mortality and DD in septic patients.

Although we were not able to include one study [29] and one conference abstract [5], they contained a total population of 39 patients which would have accounted only for 6.1 % of the study population. Moreover, both concluded that DD was associated with mortality and therefore the inclusion of these studies would have probably further strengthened our findings. Another study with a population of 25 patients was excluded because it reported the diastolic function assessment without TDI criteria [28]; the inclusion of this study did not change our main finding. Nonetheless, when comparing isolated DD only or combined SD + DD vs normal LV function, we found only trends towards higher mortality ($p = 0.10$ and $p = 0.05$, respectively). We think this could be explained by the lower number of patients included since subgroups data were available for five studies only. In fact, the overall analysis included 636 patients, while the subgroup analyses contained a sensibly lower amount of data (398–62.6, and 301–47.3 %, respectively).

Importantly, from the studies analysed we found that almost half of the patients had DD and half of the studies reported at least 50 % of patients with any degree of DD. A study in the paediatric population found an incidence of DD of 50 % among children with septic shock [31].

Despite the possibility of some methodological variability in the assessment of DD between the selected studies, we think that the findings of our meta-analysis are robust and reliable. Indeed, DD was assessed using the tissue Doppler imaging (TDI) E′ velocity, a parameter which exhibits less preload dependency [19]. This is particularly important in patients with severe sepsis and septic shock since their left atrial and ventricular diastolic filling pressures may show considerable variation in response to the insult and consequent fluid resuscitation. The TDI parameters are reliable predictors of DD (low E′ values and high E/E′ ratio), and more recently have been found to predict fluid responsiveness in septic patients [32]. This is not surprising as the E/E′ ratio is strongly correlated to left atrial pressure (also in patients with septic shock) [33], and raised left atrial pressure may predict poor responsiveness to volume expansion. A TDI method for assessing DD has been also used in the paediatric population by Raj et al. [31], but they did not find association between DD and mortality. More studies are desirable before routinely introducing TDI parameters in clinical practice as a tool for evaluating fluid responsiveness, but this method seems interesting for its simplicity and reproducibility.

Since the identification of the significance of non-invasive assessment of LV diastolic filling [34], there has been a growing interest in DD. The findings of our meta-

Table 4 Summary of quantitative analyses findings

Outcome analysed	No. of studies	No. of patients	Point estimate RR (95 % CI)	*p* value	Group heterogeneity	
					I^2	x^2p value
DD vs no DD (TDI data only)	7	636	1.82 (1.12–2.97)	0.02	77 %	0.0002
DD vs no DD (with non-TDI data)	8	661	1.84 (1.19–2.83)	0.006	73 %	0.0004
SD vs no SD	5	581	0.93 (0.62–1.39)	0.73	68 %	0.02
Isolated DD vs normal LV	5	398	2.02 (0.87–4.69)	0.10	87 %	<0.0001
Isolated SD vs normal LV	5	295	1.11 (0.66–1.89)	0.69	43 %	0.14
SD + DD vs normal LV	5	301	2.06 (1.00–4.27)	0.05	78 %	0.001

DD diastolic dysfunction, *SD* systolic dysfunction, *TDI* tissue Doppler imaging, *RR* risk ratio

analysis are not surprising considering the burden of DD in other clinical settings. Indeed, Yancy et al. [10] assessed over 100,000 hospitalizations from the Acute Decompensated Heart Failure National Registry and found that isolated DD was present in over 50 % of the hospitalizations for HF assessment. In a cross-sectional survey of over 2,000 residents aged 45 or older, Redfield et al. showed a prevalence of any grade of DD of 28.1 %, while SD was far less common (6 %). The authors conducted a multivariate analysis and showed that DD was a strong predictor of mortality with a hazard ratio ranging between 8.3 (mild DD) and 10.2 (moderate or severe DD) [8]. In another study of patients presenting acutely with pulmonary oedema and hypertension, Gandhi et al. found unchanged systolic function during and after the acute episode in all patients. The cause of pulmonary oedema was therefore attributed entirely to worsening DD [11]. Interestingly, two studies described the utility of DD for the identification of patients at high risk of weaning failure [35, 36].

The presence of DD is also important in preoperative assessment, predicting difficult weaning from cardiopulmonary bypass [37] and postoperative inotrope requirements after cardiac surgery [38]. In patients undergoing major vascular surgery, isolated DD was more common than isolated SD (43 vs 8 %, respectively), and only perioperative DD was an independent predictor of postoperative congestive HF and prolonged hospital stay [39]. Similarly, isolated DD was associated with 30-day cardiovascular events and long-term cardiovascular mortality in patients undergoing open vascular surgery [40].

Diastolic dysfunction negatively impacts LV filling, which becomes progressively more dependent on maintenance of adequate preload, sinus rhythm and avoidance of tachycardia. The pathophysiology of sepsis may cause serial disruption of these requirements. Furthermore, septic patients are relatively hypovolemic due to the profound vasoplegia and the increase in vascular permeability and capacitance. In fact, the suggested first-line therapy for the treatment of sepsis is to restore preload with volume expansion in case of hypotension or lactate level of 4 mmol/L or higher [18].

Septic patients are tachycardic by definition, and a higher heart rate (HR) worsens the LV filling, mainly by decreasing the diastolic time. To compensate for the decreased diastolic time, the LV relaxation process is accelerated (frequency-dependent acceleration of relaxation) [41], but this mechanism is impaired in sepsis [42]. Sepsis also causes rhythm disturbances, and in a recent study sepsis was an independent predictor of new-onset atrial fibrillation [43]. In this context, it is relevant to quote the results of a recent randomized controlled trial conducted in patients with septic shock and treated with standard treatment ± esmolol (continuous infusion, target to achieve an HR of 80–95 bpm) [44]. The authors found a significant improvement in cardiac performance, a decrease in inotropic requirements and lower mortality in the group of patients who received esmolol. It is, however, important to highlight that almost half of the patients were treated with levosimendan [45], which improves LV filling by shortening the iso-volumetric relaxation time [46].

Although esmolol infusion was beneficial in this trial, more research is needed since the study was not powered to detect a reduction in mortality. Both the reduction of HR and the anti-arrhythmic action of selective beta-blockade may have positively influenced the LV diastolic function of septic patients. Treatment with beta-blockade has been shown to improve the diastolic function of those patients with diastolic HF and normal EF [47]. In this regard, more insights may be provided by the on-going ESMOSEPSIS trial (ClinicalTrials.gov Identifier NCT02068287), in which patients will be randomized to esmolol or placebo, and will receive an echocardiographic assessment of the LV function.

Although we found no significant association between SD and increased mortality in patients with sepsis, these results should be interpreted with caution since we included only studies based on assessment of diastolic function. It is our opinion that the cut-off values for SD used by these studies (LVEF < 50 %) might be low in the context of the low systemic vascular resistance encountered in severe sepsis and septic shock, and this may warrant further investigation. Nonetheless, a recent meta-

analysis found no difference in the LVEF between survivors vs non-survivors [16]. Moreover, a recent retrospective study matched septic patients with pre-existing LV SD to a septic population with no cardiac disease, and the authors found no association between SD and mortality [48].

Limitations

This study has several limitations. First, none of the studies reported assessment of the diastolic function prior to the development of sepsis or septic shock. Therefore it is difficult to ascertain whether the sepsis itself directly worsened patients' diastolic function, although this seems reasonable in view of possible myocardial depression and of sepsis-induced tachycardia. Additionally, it was not possible to adjust our analysis for confounders such as age, mechanical ventilation, use of inotropes/vasopressors and volume of fluid resuscitation received since these parameters have not been systematically reported by the included studies in relation to the LV diastolic function. Moreover, the timing of TTE examination was different between studies and this may further increase the variability of findings.

Second, TDI was the preferred method for assessing DD in septic patients and this confirms the feasibility of this method in critically ill patients; nonetheless we found some discrepancy in the cut-off for the assessment of DD, reflecting both the complexity of the topic and the availability of several TDI parameters for routine daily practice.

Third, variables used for the evaluation of diastolic function tend to be influenced by a number of interrelated properties, including heart rate, filling pressure, ventricular systolic function and ventricular stiffness [49]. Myocardial relaxation is also influenced by extracardiac factors, including pericardial restraint and intrathoracic pressure. Among these variables, intrathoracic pressure is likely to vary widely in this cohort of patients. None of the studies included in the meta-analysis reported the intrathoracic pressures nor differentiated patients with pulmonary sepsis and/or ARDS from patients with extrapulmonary source of sepsis. The first group of patients could experience a greater impact on LV diastolic function from high airway pressures.

Fourth, we used mortality outcomes at the longest follow-up reported to aid quantitative analysis. There was, however, variation in the length of follow-up reported amongst the different studies. Two studies reported not only a 1-year mortality, but also data on 30-day [13] or hospital survival [24].

Finally, results need to be interpreted in the context of the significant statistical heterogeneity encountered in the majority of categories analysed. There is also an element of clinical heterogeneity with some of the included studies investigating specific populations of septic patients (i.e. oncological patients) [25, 26].

Conclusions

Our systematic review and meta-analysis found that diastolic dysfunction is very common in patients with severe sepsis and septic shock and it is associated with mortality. Systolic dysfunction was less common and not significantly associated with mortality in septic patients. When looking at subgroups, a trend towards higher mortality was seen in patients with isolated diastolic dysfunction or systo-diastolic dysfunction as compared with normal heart function.

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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