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EDITORIALS

Diastolic dysfunction and sepsis: the devil is in the detail

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Diastolic dysfunction is the consequence of impaired left ventricular relaxation, decreased recoil and decreased ventricular compliance.[1] Before the era of tissue Doppler imaging (TDI), pulmonary vein Doppler imaging in conjunction with transmitral Doppler, was a major tool in identifying diastolic dysfunction, also in septic shock patients.[2] Pulmonary vein Doppler assessment with a systolic (S) < diastolic (D) flow velocity supports the finding of elevated left ventricular filling pressures in a euvolaemic patient.

Since the introduction of TDI, cardiac ultrasound has become an important aid to detect diastolic dysfunction. TDI utilizes myocardial velocities with low frequency and high amplitude signals, filtered from conventional pulsed Doppler. No other imaging device provides so much information to comprehensively identify diastolic heart failure. TDI allows estimation of mitral annular velocities, including an early (e′) and late (a′) diastolic mitral annular velocity as well as systolic mitral annular velocity S, offering insight into both diastolic and systolic ventricular function. In conjunction with a transmitral Doppler pattern, providing early (E) and atrial (A) velocities and time intervals, the whole range of diastolic dysfunction can be assessed (Fig. 1). For a more detailed explanation of diastolic heart failure, the reader is referred to excellent reivews.[3 4] Briefly, E/A declines after which it increases up to a ratio >2 with the progression of diastolic dysfunction (Fig. 1). TDI shows decreased e′ with impaired relaxation, and this low velocity e′ persists through further evolution of disease.

The latest criteria for diagnosis of diastolic heart failure as stated in the guidelines of the American Society of Echocardiography (ASE) and the European Association of Cardiac imaging (EACI)[3] include four important features, obtained with TDI, colour Doppler and two-dimensional echo, which contribute to the diagnosis of diastolic dysfunction:[3] (i) lateral e′<10 cm s^{-1} or septal e′<7 cm s^{-1}; (ii) E/e′ is a measure of LV filling pressures: ≤8 suggests normal LV filling pressures whereas ≥14 implies increased filling pressures; (iii) presence of tricuspid regurgitation, suggesting augmented pulmonary artery pressures, with a tricuspid regurgitant velocity ≥2.8 m s^{-1}; and (iv) left atrial larger than right atrial size, implying chronically elevated LV filling pressures. These criteria suggest that a standard complete cardiac ultrasound investigation, embracing two-dimensional assessment as well as colour, pulsed, continuous wave and tissue Doppler and M mode, must be performed to detect all features of diastolic dysfunction.[3]

In the evolution from diastolic to systolic dysfunction, three clinical entities can be discerned. Diastolic failure without any heart failure is actually a preclinical stage of disease and forms the basis of a whole range of cardiac disabilities, ranging from preclinical diastolic dysfunction without any heart failure,[4] to heart failure with preserved ejection fraction, to heart failure with reduced ejection fraction and therefore overt systolic dysfunction.

Whereas diastolic dysfunction has been extensively discussed in the cardiology literature, limited information is available in the critical care setting. In this issue of the *British Journal of Anaesthesia*, Sanfilippo and colleagues are to be commended for their analysis of the existing literature on diastolic dysfunction in sepsis or septic shock.[5] As a follow-up meta-analysis of previous work,[6] they systematically reviewed the literature on diastolic dysfunction and sepsis/septic shock, analysing many studies

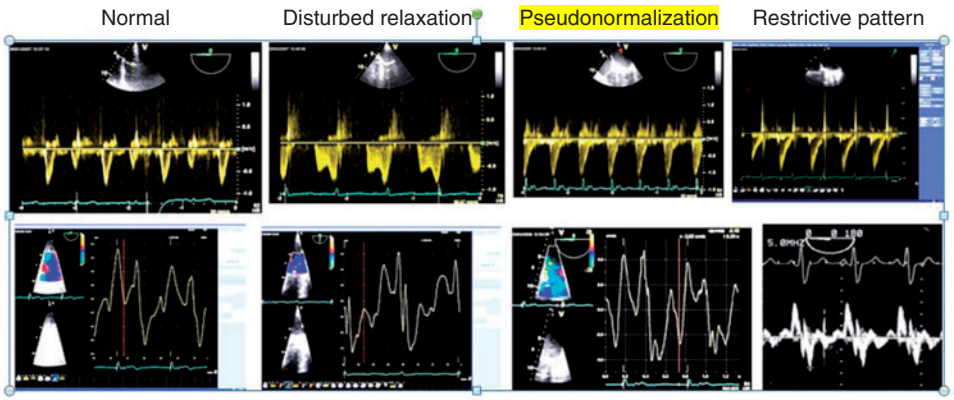

Fig 1 Diastolic Doppler patterns in the various phases of diastolic dysfunction. The upper panels show transmitral Doppler, and the lower panels TDI wave patterns. Whereas the transmitral Doppler depicts a decline with the development of a relaxation disturbance, later stages show an increase of E velocity with decreasing compliance of the left ventricle. TDI e' is always lower than a' with the progression of diastolic dysfunction.

with sometimes conflicting results. The authors made cogent conclusions, including a close relationship between a low e′, obtained in particular at the lateral border of the mitral annulus, a high E/e′ and mortality in sepsis or septic shock patients. As the cardiovascular system is a cornerstone with respect to improved survival after sepsis, both systolic and diastolic dysfunction should be considered in managing this critical illness.

The relationship between TDI variables and outcome has been assessed in the cardiology literature for many years.[7] The e′ appeared to be a powerful predictor of cardiac death in comparison with clinical data and transmitral Doppler flow velocities in a 2 yr follow-up study. In septic patients, E/e′ is the strongest independent early outcome predictor.[8] In cancer patients with septic shock, e′<8 cm s^{-1} is a strong independent predictor of mortality.[9]

There are several important aspects of this meta-analysis.[5] A strong association has been described between diastolic dysfunction and age, hypertension,[10] diabetes mellitus[11] and ischaemic heart disease.[12] The impact of these (patho) physiological interactions is not at all clarified in the analysed studies. Although e′ can be used to correct the impact of left ventricular relaxation disturbances on the early filling wave velocity E, the ratio E/e′ provides no accurate data in patients with normal function.[3] Also, this ratio can hardly be used in those patients with a calcified annulus or mitral valve disease. The latter implies indeed all studies on patients with mitral valve disease (mitral regurgitation, calcification or thickened leaflet, etc.) should be excluded from further analysis, as detailed by Sanfilippo and colleagues.[5] Caution has to be taken to assess both e′ and E/e′ where regional myocardial wall dysfunction is present. Furthermore, different cut-off values should be accepted at the septal *vs* lateral sides of the mitral ring.

The variable e′ is governed by three independent factors, namely left ventricular relaxation rate, restoring forces (reflecting diastolic suction), and inflow lengthening load (left atrial pressure at the start of mitral valve opening). The latter is influenced by early diastolic loading; left ventricular diastolic pressure during volume loading has a major impact on the untwisting rate of the left ventricle. Hence, e′ is partially influenced by volume loading, although with a decreasing impact in diminished left ventricular systolic function.[13]

What happens if E/e′ is 8–14, including a borderline e′? Cardiac ultrasound will not always provide straightforward data, as with many other monitoring techniques. The investigator is urged to reanalyse a few hours later and to monitor the evolution of the physiological variables cautiously. Important in this respect could be the combination of different cardiac ultrasound techniques.

Systolic ventricular function is closely related with the diastolic phase, because the most important determinant of early diastole is the previous systole:[1] the actively relaxing left ventricle drives blood into the ventricle during early suction, ventricular twisting and untwisting. Loss of the twisting phenomenon leads to abnormal diastolic filling, including loss of elastic recoil and thus of early diastolic intra-ventricular pressure gradients.[1] Correct insight in systolic and diastolic heart failure implies background on twisting and untwisting physiology. Viewed from the apex, twisting of the left ventricle includes a clockwise basal turning in conjunction with an anticlockwise apical rotation and is the consequence of the anatomical structure of the myofibers within the myocardium: a longitudinal trajectory in the endocardial and epicardial layers, with the midwall fibers structured in a circumferential way. Untwisting induces intraventricular pressure gradients, which add to the suction force during left ventricular filling. Details of twisting and untwisting can be assessed with speckle tracking echocardiography and provide further insight in the analysis of systolic and diastolic dysfunction. Peak systolic left ventricular twist and peak early diastolic untwisting rate are load dependent.[14] Furthermore, understanding diastolic dysfunction in the setting of critical illness is very challenging with changing vascular conditions (altering afterloading conditions, fluctuating compliance[10 15]). Much comorbidity can interfere with this clinical entity including pulmonary hypertension, respiratory insufficiency, and renal or brain failure. The new guidelines to correctly interpret the presence of diastolic failure include some of the ultrasound features to assess cardiopulmonary co-morbidities:[3] besides TDI variables e′ and E/e′, the importance of augmented

left atrial volume index (>34 ml m^{-2}) and a tricuspid regurgitant velocity (>2.8 m s^{-1}) should not be neglected.

Although it is expected that newer technology will assist in improved and early diagnosis of diastolic heart failure in sepsis and septic shock, the present meta-analysis emphasizes the close correlation between lateral e′<10 cm s^{-1} and E/e′>14 with increased mortality. Additional investigations are needed to clearly delineate the importance of the presence of a significant tricuspid regurgitation and increased left atrial volume index in the outcome of sepsis/septic shock patients. The details are extremely important with respect to accurate interpretation of cardiac ultrasound images.

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Readmission after surgery: are neuromuscular blocking drugs a cause?

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Neuromuscular blocking drugs (NMBDs) play an integral role in balanced anaesthesia. They improve intubating conditions, reduce iatrogenic damage to the upper airway and decrease postoperative hoarseness.[1] They also improve surgical operating conditions.[2] But use of NMBDs always carries the risk of residual neuromuscular block postoperatively. About 30% of all patients who receive NMBDs intraoperatively show signs of residual neuromuscular block when arriving in the post-anaesthesia care

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Review Article

Tissue Doppler assessment of diastolic function and relationship with mortality in critically ill septic patients: a systematic review and meta-analysis

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Abstract

Background: Myocardial dysfunction may contribute to circulatory failure in sepsis. There is growing evidence of an association between left ventricular diastolic dysfunction (LVDD) and mortality in septic patients. Utilizing echocardiography, we know that tissue Doppler imaging (TDI) variables e′ and E/e′ are reliable predictors of LVDD and are useful measurements to estimate left ventricular (LV) filling pressures.

Methods: We conducted a systematic review and meta-analysis to investigate the association of e′ and E/e′ with mortality of patients with severe sepsis or septic shock. In the primary analysis, we included studies providing transthoracic TDI data for e′ and E/e′ and their association with mortality. Subgroup analyses were conducted according to myocardial regional focus of TDI assessment (septal, lateral or averaged). Three secondary analyses were performed: one included data from a transoesophageal study, another excluded studies reporting data at a very early (<6 h) or late (>48 h) stage following diagnosis, and the third pooled data only from studies excluding patients with heart valve disease.

Results: The primary analysis included 16 studies with 1507 patients with severe sepsis and/or septic shock. A significant association was found between mortality and both lower e′ [standard mean difference (SMD) 0.33; 95% confidence interval (CI): 0.05, 0.62; *P*=0.02] and higher E/e′ (SMD –0.33; 95% CI: –0.57, –0.10; *P*=0.006). In the subgroup analyses, only the lateral TDI values showed significant association with mortality (lower e′ SMD 0.45; 95% CI: 0.11, 0.78; *P*=0.009; higher E/e′ SMD –0.49; 95% CI: –0.76, –0.22; *P*=0.0003). The findings of the primary analysis were confirmed by all secondary analyses.

Conclusions: There is a strong association between both lower e′ and higher E/e′ and mortality in septic patients.

Key words: diastolic dysfunction; echocardiography; intensive care; septic shock; severe sepsis

Editor's key points

- Previous data show that left ventricular diastolic dysfunction is common in sepsis and associated with worse outcome.
- New guidelines for determining LVDD by echocardiography include tissue Doppler assessment of the early myocardial diastolic e′ wave and early myocardial relaxation wave (E/e′).
- This updated systematic review includes studies reporting to the new echocardiography guidelines.
- The results confirm that LVDD as shown by decreased e′ wave and higher E/e′ ratio is strongly associated with mortality in severe sepsis.
- The significance of LVDD earlier in the evolution of sepsis remains to be established.

Sepsis results from an individual's exaggerated response to an infective process and is associated with profound haemodynamic disturbance, resulting in significant mortality and morbidity when the initial process evolves into circulatory and consequent multi-organ failure. A recent expert consensus has defined septic shock as a subset of septic disease in which the underlying circulatory, cellular and metabolic disturbances are associated with a higher mortality.[1–3] Septic shock is characterized by profound vasoplegia requiring administration of vasoactive agents to maintain organ perfusion.[4] It has become more evident over the past decade that septic patients may exhibit pronounced myocardial dysfunction,[5 6] which could possibly be the result of increased circulating catecholamine and cytokine levels.[7 8] Septic myocardial dysfunction may involve either the left ventricle (LV), the right ventricle (RV) or both. This may manifest as systolic dysfunction,[8] and also as reversible LV diastolic dysfunction (LVDD).[9] A meta-analysis by Huang and colleagues[10] has shown no association between LV or RV systolic dysfunction and mortality in patients with severe sepsis or septic shock, when systolic function is evaluated by ejection fraction. A previous meta-analysis from our group of investigators has demonstrated an association between LVDD and mortality in the same population. We also confirmed the finding of Huang and colleagues[10] showing that there is no association between left ventricular ejection fraction (LVEF) and mortality in septic patients.[11 12] One of the limitations of our previous meta-analysis was the inclusion of only seven studies. Since this publication, a number of further studies in critically ill patients have been published. In addition, our previous work investigated only the effect of abnormal diastolic function, but the recently revised guidelines[13] have significantly changed the methodology for determining LVDD.[14] These recommendations are now based on the assessment of four variables: tricuspid regurgitation jet velocity, left atrial volume, e′ wave, and E/e′ ratio.[13] We feel that it is important to use all the information available from current research to investigate some of the implications of the new guidelines. This provides part of the rationale for this new meta-analysis.

Importantly, the interpretation of echocardiographic measurements in septic patients is challenging because of the variable ventricular loading conditions. Tricuspid regurgitation and left atrial volume may be significantly influenced by mechanical ventilation and loading conditions. As these variables are only included in these latest guidelines and are rarely reported, we have not included them in this study. We focused on tissue Doppler imaging (TDI) and we feel that the increased reliance on these variables is to be welcomed, because of their relative load independency[15] as compared with blood pool Doppler. The early myocardial diastolic e′ wave provides information on myocardial velocity at the mitral annulus level, and cut-offs of <7 cm s^{-1} for septal and <10 cm s^{-1} for lateral tissue velocity are considered as abnormal, although using average e′ value should be the preferred approach.[13] The second TDI-derived variable included in the new algorithm for grading LVDD is the ratio of the early transmitral pulse-wave Doppler flow to the early myocardial relaxation wave (E/e′). This variable correlates with left atrial pressure (LAP) and pulmonary capillary wedge pressure, and a value below 8 correlates with non-elevated LAP, whereas an averaged ratio above 14 indicates raised left-sided filling pressures.[13] E/e′ ratio has shown good predictive value of LV filling pressures in patients with septic shock,[16] although some controversies remain in patients with heart failure and severe LV systolic dysfunction.[17–19]

Many studies report TDI variables according to survival in septic patients but with conflicting results. We aimed to investigate the predictive value for survival between these two TDI-derived variables in patients with severe sepsis and/or septic shock. The primary hypothesis of our meta-analysis was that lower e′ and higher E/e′ are significantly associated with mortality in this population of patients.

Methods

We conducted this systematic review and meta-analysis in accordance with the PRISMA guidelines[20] and registered our project with the international prospective register of systematic reviews (PROSPERO – number CRD 42016041712).

Eligibility criteria and identification of studies

The definition of sepsis and septic shock has changed only recently. We therefore included observational studies providing data on mortality of patients with severe sepsis and/or septic shock as defined by the previous international consensus.[21] Studies were included if they provided one or both TDI variables (e′ and/or E/e′), comparing values in survivors and non-survivors. We accepted studies providing values from the septal or lateral annular region as well as averaged TDI values. Inclusion criteria for clinical studies were pre-specified using the PICOS format (Table 1). Exclusion criteria were studies on those under 18 yr and case series reporting data and outcomes from less than 10 patients. By consensus, we only included studies reporting data obtained with transthoracic echocardiography in the primary analysis, but we considered transoesophageal studies in a secondary analysis.

We performed a systematic search of two electronic databases—MEDLINE (PubMed) and EMBASE—using the *NHS Healthcare Databases Advanced Search* tool. Relevant findings were also recognized by manual searching of reviews on the topic and exploring the list of the references of the included studies. We started our search from inception of MEDLINE (PubMed) database, while findings retrieved from EMBASE as conference abstracts were considered only if published after June 2013 to allow a reasonable time for adequate peer-review process. Only articles published in English, Spanish, French, German or Italian were considered. Duplicates were filtered

Table 1 'PICOS' approach for selecting clinical studies in the systematic search. TDI, tissue Doppler Imaging

PICOS	Characteristics of clinical studies included in the qualitative synthesis and meta-analysis
1. Participants	Adult patients with severe sepsis and/or septic shock.
2. Intervention	Echocardiographic TDI assessment with transthoracic echocardiography.
3. Comparison	Primary: comparison between survivors and non-survivors of e′ and/or E/e′. Subgroup analyses: conducted according to the regional focus of TDI assessment (septal, lateral, average). Secondary analyses: (1) including results of transoesophageal studies; (2) excluding studies with very early (≤6 h) or late (>48 h) assessment; and (3) excluding studies enrolling patients with heart valve disease. Sensitivity analyses: 'leaving-one-out' approach; excluding studies with intermediate or high risk of bias.
4. Outcomes	Mortality (at longest follow-up available).
5. Study design	Prospective clinical studies. Case series only if including more than 10 patients.

through automated function and then manually searched. The last search update was on September 11, 2016.

Initially, the findings of two search groups were combined: the items 'respiratory distress syndrome', 'sepsis', 'septic shock', 'systemic inflammatory response' (Thomson Reuters, Philadelphia, PA USA) were used for the first group; the terms 'Doppler Tissue' and 'Tissue Doppler' (Thomson Reuters, Philadelphia, PA USA) for the second group. As many studies were expected to report echocardiographic variables in the main text but not in the abstract/title or key words, the above 'restrictive' search strategy was coupled with a more liberal one including generic words: 'echocardiograph*', 'ejection fraction', 'diastolic function' and 'diastolic dysfunction', 'systolic function' and 'systolic dysfunction'. References were managed using Endnote X7 citation manager (Thomson Reuters, Philadelphia, PA USA).

Study selection and data extraction

Three authors (F.S., C.C. and A.A.) independently reviewed the findings of the electronic search and selected abstracts and potentially relevant articles for the topic of interest. Articles potentially relevant were downloaded and then assessed against the eligibility criteria. Any discrepancy in an author's opinion on the inclusion of an article was resolved by consensus and/or by involving the other authors (G.L., M.C., A.V.-B. and N.F.). Two reviewers (F.S. and C.C.) independently extracted the data from each study, which were recorded into a pre-defined collection sheet. Data extracted from each study included the number of septic patients examined, the percentage of patients mechanically ventilated, the severity scores and the longest follow-up data on mortality, as shown in Table 2. A list of all the inclusion and exclusion criteria is provided separately as Supplementary data, Digital Content S1.

In the case of articles with missing data on one or both TDI variables, we contacted the corresponding author (and/or co-authors) via e-mail to check the availability of such data. All of the authors also conducted an independent search on MEDLINE (PubMed) to check for further evidence before the final editing of the manuscript.

Quality assessment of study design

Methodological quality of included observational studies was assessed using the Newcastle–Ottawa scale (NOS). The NOS explores risk of bias in three different domains: selection, comparability and outcome. A maximum cumulative score of 9 points can be obtained and studies are classified as high-risk (1–3 points), intermediate-risk (4–5 points) or low-risk of bias (6–9 points).[22]

Analysis of outcomes

The primary analysis investigated the differences between e′ and E/e′ ratio among surviving and non-surviving septic patients. In the case of studies providing both the septal and the lateral values, we asked the corresponding author to provide averaged data, which we used for the overall analysis. As studies were expected to report mortality at different time intervals, we used the values of the longest follow-up. We also performed subgroup analyses for each variable according to the myocardial 'regional' focus used for TDI evaluation (septal, lateral, averaged values).

Three secondary analyses were conducted: the first one included results reported with transoesophageal echocardiography; the second one was performed excluding studies with very early (≤6 h) or late (>48 h) TDI assessment; and the third one was conducted including only studies that excluded patients with heart valve disease. We planned two sensitivity analyses of the primary outcome: one performing the analysis multiple times with 'leaving-one-out' at time approach; and another conducted excluding studies with intermediate or high risk of bias.

Statistical analysis

Mean values and standard deviation (SD) of the variables of interest were collected for the outcome analysis. If data were reported only as median and interquartile range (IQR) or confidence interval (CI), we followed published and online Cochrane's recommendations to approximate the values of mean and SD.[23–25]

Continuous outcome differences were analysed using an inverse variance model with a 95% CI. We reported values using standard mean difference (SMD), and *P*-values were two-tailed and considered significant if <0.05. Negative values of SMD indicated that lower values of the TDI variable were associated with higher survival, whereas positive values of SMD indicated that higher values of the TDI variable were associated with higher survival. The presence of statistical heterogeneity was assessed using the X^2 (Cochran Q) test. Heterogeneity was likely if $Q > df$ (degrees of freedom), and confirmed if $P \leq 0.10$. Quantification of heterogeneity performed using I^2 statistic. The degree of heterogeneity was defined as none, low, moderate or high according to I^2 values of 0%–24.9%, 25%–49.9%, 50%–74.9% and >75%, respectively.[26] If heterogeneity was quantified as low or above, a random model was used.

Table 2 Characteristics of studies included in the meta-analysis. Severity scores are reported according to the version of scoring adopted by the authors, and in brackets are reported values of standard deviation or interquartile range as reported in the study. Data on the number of patients on mechanical ventilation (MV) are reported, if available, at the time of echocardiographic assessment. ED, Emergency Department; ICU, Intensive Care Unit; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography; SOFA, sequential organ failure assessment; SAPS, simplified acute physiology score; APACHE, acute physiological assessment and chronic health evaluation. *Authors provided the average data, whereas the papers report both septal and lateral values, which were used for secondary analysis according to regional criteria. †Authors provided data: missing 11 survivors and 2 non-survivors. Data according to septal criteria. ‡Authors provided data excluding 16 patients with sepsis

Author/year	Population (n=)	TTE *vs* TOE	Data provided	MV (%)	SAPS SOFA APACHE	Mortality (%)	Longest follow-up
Brown, 2012	78 ICU patients with severe sepsis or septic shock	TTE within 6 h of ICU admission	e′ – E/e′ (septal)	43.6	– – 23.3 (7.4)	16.5	28 days
Chang, 2015	111 ICU patients with septic shock	TTE within 24 h of ICU admission	e′ – E/e′ (average)	65.8	– – 21 (8)	35.1	Hospital
De Geer, 2014	50 ICU patients with septic shock	TTE within 24 h of ICU admission	e′ – E/e′ (septal)	84	– 11 (9–12) –	34	90 day
Etchecopar-Chevreuil, 2008	35 ICU patients with septic shock	TEE within 12 h of ICU admission	e′ only (lateral)	100	53 (46–62) 9 (8–11) –	25.7	ICU
Gonzalez, 2016	223 ICU patients with septic shock	TTE* within 24 h of shock onset	e′ – E/e′ (lateral)	91	55 (18) 10 (3) –	35	ICU
Ikonomidis, 2014	70 ICU patients with septic shock	TTE* within 48 h of ICU admission	e′ – E/e′ (average)	100	– 7.6 (3.2) 17.5 (5.2)	48.6	ICU
Landesberg, 2012*	262 ICU patients with severe sepsis or septic shock	TTE 1.6±0.9 days after ICU admission	e′ – E/e′ (septal and lateral)	100	– 9.52 (3.8) 20.98 (7.1)	36	Hospital
Landesberg, 2014*	106 ICU patients with severe sepsis or septic shock	TTE on the day of ICU admission or as early as possible	e′ – E/e′ (septal and lateral)	100	– – 21.61 (6.8)	39	Hospital
Lanspa, 2016	174 ICU patients with severe sepsis or septic shock	TTE within 24 h of diagnosis	e′ – E/e′ (septal)	36.8	– 8 (6–11) 25 (18–33)	23.6	28 day
McLean, 2007	40 ICU patients with severe sepsis (18) or septic shock (22)	TTE within 2 h of ICU admission	e′ – E/e′ (lateral)	73	– – 20.7 (7.1)	23	Hospital
Mourad, 2014	72 ICU patients with septic shock	TTE within 48 h of diagnosis	e′ – E/e′ (lateral)	42	57 (46–69) 11 (9–13) –	48.6	ICU
Pulido, 2012†	93 ICU patients with severe sepsis or septic shock*	TTE within 24 h of ICU admission	e′ – E/e′ (septal)	10	– 11.1 (3.7) 88.3 (29.1)	35.8	30 day
Rolando, 2015	53 ICU patients with severe sepsis (30) or septic shock (23)	TTE within 48 h of ICU admission	e′ – E/e′ (lateral)	85	– 7 (3) 19 (5)	66	ICU
Santos, 2015‡	47 ED patients with severe sepsis or septic shock	TTE before or within 5 min of fluid challenge	e′ – E/e′ (lateral)	0	58.9 (21.5) 7.9 (4.31)	19	28 day
Sturgess, 2010	21 ICU patients with septic shock	TTE 1.9±0.7 days after onset of septic shock	e′ – E/e′ (septal)	76	– 11 (2.8) 80.1 (23.8)	29	Hospital
Weng, 2012	61 ICU patients with septic shock	TTE within 24 h of shock onset	e′ – E/e′ (average)	100	– 10 (8–12) 84 (68–97)	39.3	90-day
Zaky, 2016	53 ICU patients with sepsis and/or septic shock	TTE within the first week of diagnosis	E/e′ only (lateral)	N/A	– 9.3 (6.2) –	37.7	Hospital

Two sensitivity analyses were planned: the first one excluded studies with intermediate and high risk of bias; and another was performed with 'leaving-one-out' at time approach. Publication bias was investigated using the Egger's regression asymmetry test and a $P<0.05$ was considered to be suggestive of a statistically significant publication bias.[27] Meta-analysis was performed using review manager (Revman) for MAC (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The Egger's regression test was performed to verify the presence of publication bias using the comprehensive meta-analysis version 2.2.064.

Results

Study selection

The literature search on Medline produced 29 titles for the restrictive search strategy and 1069 titles for the more liberal search approach. No additional articles were found by an independent search. After screening all of the articles, only 39 studies were identified as potentially relevant and full-text was retrieved. Twenty-one studies were excluded; thus, the 18 remaining papers were selected for the qualitative analysis from Medline.[28–45]

The search on EMBASE restricted to studies published after 2013 produced 13 and 755 titles for the restrictive and the liberal approach, respectively. One international conference abstract not yet available in Medline provided unspecified E/e′ values in the target population of our study. We were not able to contact the authors (Sanchez-Ruiz and colleagues, abstract 0950, Paris ESICM LIVES 2013) and the abstract was not included. Therefore, the search on EMBASE did not add further evidence to the Medline findings.

Of the 18 studies included in the qualitative synthesis, 10 had unclear or missing data on e′ and/or E/e′ (most of them reporting values for only one of the two variables). We managed to retrieve data from all of these papers, although in one study, the authors provided only E/e′ values and they did not respond to a request for e′ values; therefore, we had to include only the E/e′ results from this study.[43] Two of these studies included both patients with sepsis, severe sepsis and septic shock,[40 44] but only one group of authors provided reliable values including only patients with severe sepsis and septic shock (thus excluding those with sepsis). Therefore, only one study was included in the analysis,[40] while the other was excluded from the quantitative synthesis,[44] leaving finally 17 studies. One study was conducted with transoesophageal echocardiography; this study reported only e′ values and was included in the secondary analysis for e′ values only because the corresponding authors could not provide data on E/e′.[31] Therefore, 16 studies included in the meta-analysis provided transthoracic echocardiography data on TDI values, and were thus used for the primary analysis. In particular, 15 studies compared e′, and all 16 provided results on E/e′.

The PRISMA flowchart of our systematic search and qualitative synthesis is shown in Figure 1. The characteristics of all of the studies included in the primary and secondary analyses are summarized in Table 2. Methodological quality of all included studies was deemed to be of low risk of bias when analysed using the Newcastle–Ottawa scale (Supplementary data, Digital Content S2). All the results of the meta-analyses are summarized in a Table 3.

Overall and subgroups analysis of e′

Fifteen observational studies in patients with severe sepsis and/or septic shock provided values of e′ between survivors (n=940) and non-survivors (n=514) for an overall mortality of 35.4% at longest follow-up. Five studies examined only septal values,[28 30 36 38 41] five studies used lateral e′,[32 37 39 40 45] and in three of them e′ values were averaged.[29 33 42] Finally, two studies provided e′ values for both septal and lateral,[34 35] and the first author provided the averaged data, which were used for the primary analysis. Overall, survivors showed a significantly higher e′ (SMD 0.33; 95% CI 0.05, 0.62; P=0.02, Fig. 2) with high overall heterogeneity (I^2=82%) and low heterogeneity for subgroups differences (I^2=41.8%, P=0.18).

Three subgroup analyses were conducted investigating the isolated septal, lateral and average subgroups, and such analyses also included data from the septal and lateral e′ TDI provided by the two studies by Landesberg and colleagues[34 35] These analyses showed no correlation between mortality and lower septal e′ velocity (seven studies; SMD 0.25; 95% CI –0.12, 0.62; P=0.18; high heterogeneity, I^2=79%, $P<0.0001$), whereas a borderline association was found for average e′ values (five studies; SMD 0.55; 95% CI 0.00, 1.10; P=0.05; high heterogeneity, I^2=89%, $P<0.00001$). Lower lateral e′ values showed a significant association with mortality (seven studies; SMD 0.45; 95% CI 0.11, 0.78; P=0.009; high heterogeneity, I^2=76%, P=0.0004). Forest plots of these analyses are provided as Supplementary data, Digital Content S3–S5.

Overall and subgroups analysis of E/e′ ratio

Sixteen observational studies provided values of E/e′ ratio between survivors (n=973) and non-survivors (n=534) among patients with severe sepsis and/or septic shock (mortality 38.4% at longest follow-up). Respectively, five,[28 30 36 38 41] six[32 37 39 40 43 45] and three[29 33 42] studies reported E/e′ ratios according to septal, lateral or averaged examinations. Again, the two studies by Landesberg and colleagues[34 35] reported separately E/e′ ratios for both septal and lateral TDI and the averaged data provided by the author were used for the primary analysis, whereas the isolated septal and lateral values were used for the subgroups analysis. Overall, survivors exhibited a significantly lower E/e′ ratio (SMD –0.33; 95% CI –0.57, –0.10; P=0.006, Fig. 3) with high overall heterogeneity (I^2=76%) but no heterogeneity between subgroups (I^2=0%, P=0.60).

Three subgroup analyses were conducted investigating the isolated septal, lateral and average subgroups, and including septal and lateral E/e′ TDI data from the two studies by Landesberg and colleagues.[34 35] These analyses demonstrated no significant correlation between survival and higher septal E/e′ (seven studies; SMD –0.28; 95% CI –0.74, 0.18; P=0.23; I^2=83%) or average E/e′ (five studies; SMD –0.24; 95% CI –0.55, 0.06; P=0.12; I^2=67%). A significant association was found between mortality and higher lateral E/e′ (eight studies; SMD –0.49; 95% CI –0.76, –0.22; P=0.0003; I^2=62%). Forest plots of these analyses are provided as Supplementary data, Digital Content S6–S8.

Secondary analyses

The inclusion of the only study using transoesophageal echocardiography data on e′[31] did not affect results of the primary analysis (SMD 0.31; 95% CI 0.04, 0.58; P=0.03; high overall heterogeneity, I^2=81%).

Another secondary analysis was conducted excluding a total of four studies because of the timing of echocardiographic

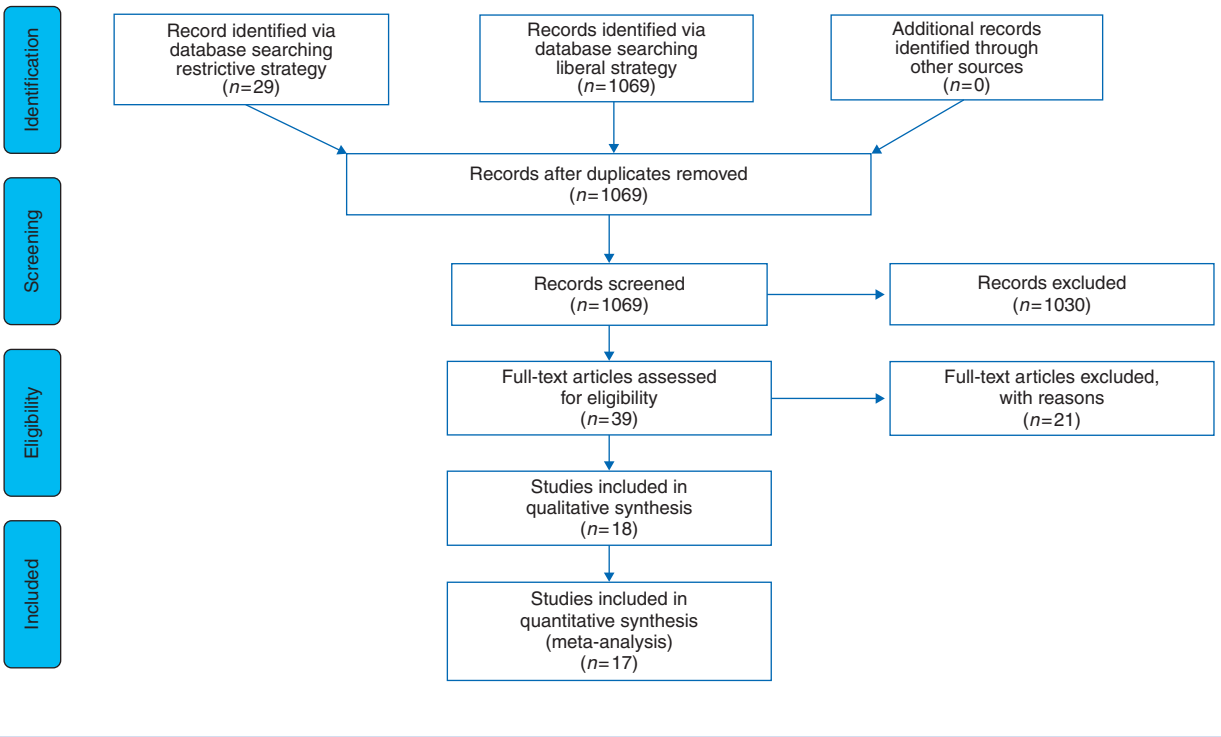

Fig 1 Flowchart of study selection according to the PRISMA guidelines.

Table 3 Summary of the results of primary, subgroups and secondary analyses. SMD, standard mean difference

Comparison	Outcome	*n* of studies	SMD	*P*	I^2 (%)
Primary and subgroups analyses: e′ values and survival at longest follow-up	Overall e′	15	0.33 (0.05, 0.62)	0.02	82
	Lateral e′	7	0.45 (0.11, 0.78)	0.009	76
	Septal e′	7	0.25 (−0.12, 0.68)	0.18	79
	Average e′	5	0.55 (0.00, 1.10)	0.05	89
Primary and subgroups analyses: E/e′ values and survival at longest follow-up	Overall E/e′	16	−0.33 (−0.57, −0.10)	0.006	76
	Lateral E/e′	8	−0.49 (−0.76, −0.22)	0.0003	62
	Septal E/e′	7	−0.28 (−0.74, 0.18)	0.23	83
	Average E/e′	5	−0.24 (−0.55, 0.06)	0.12	67
Secondary analysis: including one TEE study	Overall e′	16	0.31 (0.04, 0.58)	0.03	81
Secondary analysis: according to timing of assessment	Overall e′	12	0.38 (0.10, 0.66)	0.008	81
	Overall E/e′	12	−0.36 (−0.59, −0.13)	0.002	71
Secondary analysis: studies excluding patients with heart valve disease	Overall e′	10	0.37 (0.03, 0.71)	0.03	80
	Overall E/e′	11	−0.47 (−0.80, −0.13)	0.006	80

assessment. Three of the studies conducted a very early assessment [in the emergency department,[40] within 2 h[45] and within 6 h of intensive care unit (ICU) admission[28]] or a late evaluation (performed up to one week from ICU admission[43]) These analyses did not show significant changes in the results of the overall primary outcome (both remaining significant: e′, SMD 0.38; 95% CI 0.10, 0.66; P=0.008; I^2=81%; E/e′, SMD –0.36; 95% CI –0.59, –0.13; P=0.002; I^2=71%).

The third secondary analysis was performed with data from the studies excluding patients with heart valve disease (see Supplementary data, Digital Content S1). Both analyses for the two variables of interest confirmed a significant association between mortality and lower e′ (SMD 0.37; 95% CI 0.03, 0.71; P=0.03; I^2=80%) and higher E/e′ (SMD –0.47; 95% CI –0.80, –0.13; P=0.006; I^2=80%).

Sensitivity analyses and publication bias

The sensitivity analyses conducted by performing a ‘leave-one-out’ approach did not change the results of E/e′ ratio analysis.

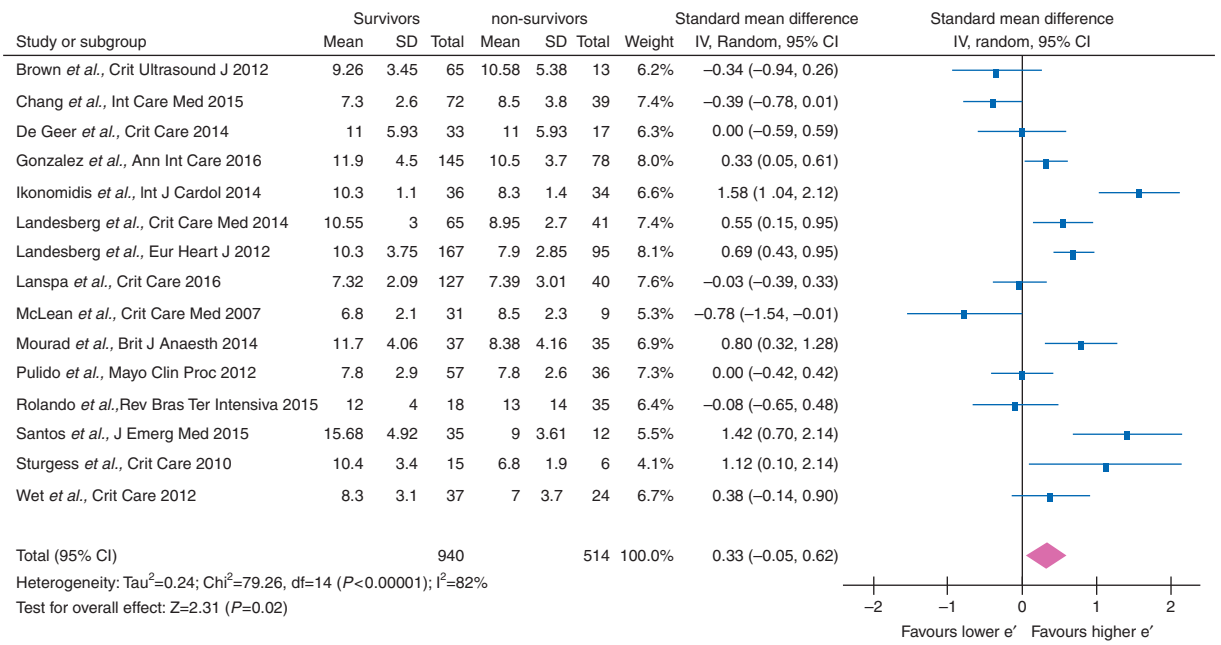

Fig 2 Forest plot comparing e′ values between survivors and non-survivors among patients with severe sepsis and/or septic shock. Studies are grouped according to the regional criteria for evaluation of e′ (septal, lateral or average).

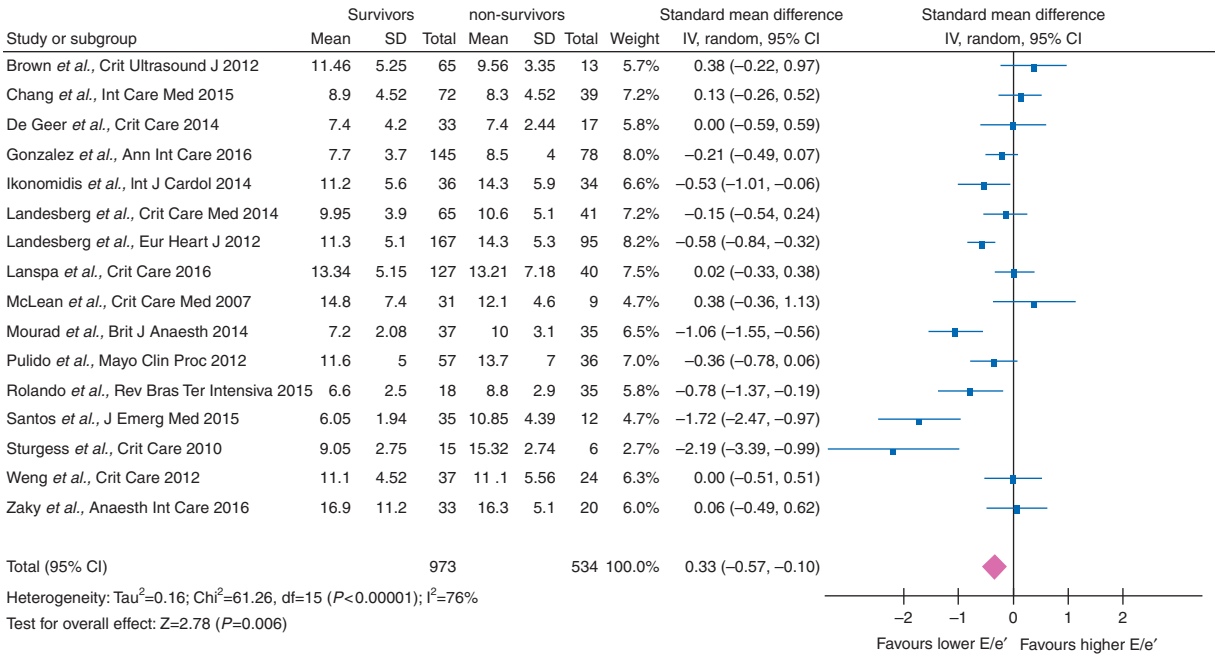

Fig 3 Forest plot comparing E/e′ values between survivors and non-survivors among patients with severe sepsis and/or septic shock. Studies are grouped according to the regional criteria for evaluation of e′ for the E/e′ ratio calculation (septal, lateral or average).

Most of the results on e′ remained unchanged in these sensitivity analyses, although the exclusion of data from any of the four studies[33 34 37 40] resulted in a non-significant trend towards higher mortality in patients with lower e′ (*P*-value ranging between 0.05 and 0.06). As all of the studies had a low risk of bias according to the NOS tool (score ranging between 6 and 9), we did not perform a further sensitivity analysis according to the quality of study design.

No evidence of publication bias was found for both analyses according to Egger's test (e′, *P*=0.61; E/e′, *P*=0.48).

Discussion

Our meta-analysis investigated the association of e′ and E/e′ with mortality in patients with severe sepsis and/or septic shock, including up to 16 studies in the primary analysis. We found a significant association between mortality and both overall lower e′ and higher E/e′ values in patients with severe sepsis and/or septic shock. These findings build on our previous work and further support the hypothesis of an increased risk of death in critically ill septic patients with LVDD.[11 12] It is difficult to draw conclusions about the degree of diastolic function in critically ill patients with reference to the recent revised guidelines as we could not take left atrial volume and velocity of tricuspid jet regurgitation into account.[13] Tricuspid regurgitation velocity may vary with mechanical ventilation, whereas left atrial volume is influenced by the loading conditions and it is unlikely to reliably reflect a sudden deterioration of LV diastolic function as a result of septic myocardial dysfunction. Therefore, the assessment of LVDD in critically ill patients remains challenging and the evaluation of e′ and E/e′ is probably the most useful tool in this regard. Despite the use of differing assessment criteria for TDI assessment in the included studies (septal, lateral, averaged), we believe that such variability is unlikely to influence the clinical meaning of our results. We think that our findings are robust and reliable and we consider that TDI assessment serves as a useful prognostic tool in the early stages of severe sepsis or septic shock. Indeed, e′ velocity exhibits less preload dependency,[15] which is particularly relevant in this population, as LAP and LV diastolic filling pressures may show considerable variation in response to the insult severity and heart rate. Indeed, fluid and pharmacological therapies administered, and the timing of echocardiography further complicate assessment of diastolic function. However, it should be noted that in the analysis performed according to regional TDI criteria, only the assessment of e′ and E/e′ ratio at the lateral mitral annulus was associated with increased mortality. There was only a trend for an association between mortality and the septal (e′, *P*=018; E/e′, *P*=0.15) and average values (e′, *P*=0.05; E/e′, *P*=0.12). It is interesting to note that in two studies conducted in patients with normal LVEF, lateral E/e′ had the best correlation with LV filling pressures and invasive indices of LV stiffness.[46 47] Nonetheless, this result should to be interpreted with caution as it could be due just to the higher sample size in the subgroup assessed with lateral criteria (over 850 patients in total) as compared with the other two subgroups (777 and 610 patients for the septal and the average evaluation, respectively). It is also possible that ongoing RV dysfunction/failure has a greater degree of interaction with septal TDI velocities compared with lateral values. Indeed, RV dysfunction/failure may be present in a significant proportion of patients with severe sepsis and septic shock, and it is significantly impacted by mechanical ventilation strategy;[48 49] a variable that we were unable control for. Nonetheless, the LV and RV are interdependent, and averaging septal and lateral TDI values remains the recommended approach.

It is likely that e′ and E/e′ ratio also show alterations at early stages of sepsis. In the study by Santos and colleagues,[40] patients admitted to emergency department with a diagnosis of sepsis at any stage received early echocardiographic assessment. The authors found that patients with septic shock showed significantly lower e′ values when compared with those with sepsis. The progressive increase of E/e′ ratio was even more significant when comparing patients with sepsis *vs* severe sepsis *vs* septic shock (*P*=0.001 for all comparisons). In this study, the commonly adopted cut-offs of e′ ($<8\,cm\,s^{-1}$) and E/e′ (ratio >8) clearly differentiated septic patients with higher severity scores.[40] This finding supports a progressive deterioration of LV diastolic function with evolving septic stages, although a smaller study did not find a significant difference between sepsis and severe sepsis/septic shock.[44] More research into the evolution of LVDD during episodes of sepsis is needed.

Both TDI variables can be easily and rapidly assessed and their utility is not only prognostic. For instance, low e′ values and high E/e′ ratio are not only reliably associated with LVDD, but their variation has been correlated with fluid responsiveness; in particular, a higher increase of e′ velocity has been shown in fluid-responsive septic patients, whereas a greater variation of E/e′ has been noted for patients with no fluid responsiveness.[50] Such a finding is not surprising; for instance, E/e′ ratio strongly correlates to LAP[16] and an already increased LAP should warrant caution on further volume expansion. More evidence is needed before recommending routine TDI assessment of diastolic function as a clinical tool for indicating volume expansion, but this approach is attractive for its reproducibility and ease of use.

Diastolic dysfunction may continue to have an effect on patient recovery after the acute septic episode has attenuated. Three studies described the utility of E/e′ for the identification of patients at high risk of weaning failure,[51–53] showing that impaired diastolic function delays separation from the ventilator and raises the possibility that it may also contribute to late ICU and in-hospital death.

Patients with LVDD are likely to have impaired LV filling, which progressively relies on maintenance of preload, avoidance of tachycardia and significant arrhythmias. The septic process causes sequential disturbances at these levels. Septic patients are relatively hypovolemic because of vasoplegia and increased capillary permeability and higher venous capacitance. In fact, the recommended first-line therapy for the treatment of sepsis is to restore preload.[21] Tachycardia further worsens LV filling, mainly by a disproportionally reduced diastolic time. Although healthy individuals compensate by accelerating the LV relaxation process (frequency-dependent acceleration of relaxation),[54] this process is impaired during sepsis.[55] Furthermore, sepsis is independently associated with new-onset atrial fibrillation,[56] which in turn worsen LV filling by eliminating atrial contraction. With such a background, it is interesting to interpret the beneficial effects of esmolol infusion in septic shock patients,[57] where authors found a significant improvement in cardiac performance, lower inotropic requirements and higher survival in the group treated with esmolol. Both the negative chronotropic and the anti-arrhythmic effects of selective beta-blockade may have positively influenced the LV diastolic function of these patients. However, it should be noted that almost half of the population received levosimendan,[58] which has positive effects on LVDD,[59] and that authors did not present any echocardiographic data. On the other hand,

the same group of authors recently showed an improved LV filling pattern and ventriculo-arterial coupling after esmolol infusion in septic patients.[60] We also know that in patients with isolated diastolic heart failure (HF) diastolic function improves with beta-blockade treatment.[61]

The TDI variables have been also used in the paediatric population for assessing LVDD. One study found an incidence of LVDD of 50% among children with septic shock,[62] although a standardized definition of LVDD is still missing. The study reported a mortality below 7%, thus the association between myocardial dysfunction and mortality should be investigated by larger studies before making any firm conclusion.

The findings of our study are consistent with the significance of LVDD in other clinical settings. It has been found that in patients presenting to the hospital with pulmonary oedema and hypertension, up to 50% have unchanged systolic function during and after the acute episode.[63] Similarly, the incidence of isolated LVDD may be higher than 50% in patients hospitalized for heart failure.[64] Redfield and colleagues[65] showed that LVDD was up to five times more frequent than LV systolic dysfunction (28% *vs* 6%, respectively) in patients aged 45 or older; moreover LVDD was a strong predictor of mortality with a hazard ratio ranging from 8.3 (mild LVDD) to 10.2 (at least moderate LVDD).

Determination of the presence of LVDD is also crucial during preoperative assessment. In cardiac surgery patients, it correlates with prolonged weaning from cardiopulmonary bypass[66] and higher postoperative inotropic requirements.[67] In patients undergoing major vascular surgery, isolated LVDD is more frequent than isolated LV systolic function (43% *vs* 8%, respectively) and, importantly, LVDD is an independent predictor of postoperative HF and prolonged hospital stay,[68] and it is associated with postoperative adverse cardiovascular events and long-term cardiovascular mortality.[69]

Strengths and limitations

One strength of our meta-analysis is the inclusion of very recent studies, most of them published within the last four years; the results were also unchanged by the *post hoc* analysis, which excluded three relatively older papers (2007, 2008, 2010).[31 41 45] Another strength is that we have increased the sample size by contacting authors in order to get more data (see the Acknowledgments section). Our study is timely, as the very recent changes in the international consensus on sepsis definition is likely to change the characteristics of this cohort of patients, which may introduce a selection bias in future meta-analysis.

Another strength of this meta-analysis is that it did not rely on variable definitions of LVDD as did our previous meta-analysis.[11 12] The present analysis included a greater number of patients and studies, and its results were confirmed by the sensitivity analyses. Other strengths are the absence of publication bias according to Egger's test, although a significant statistical heterogeneity was seen in the overall tests, and another element of clinical heterogeneity is present as some studies may have included only specific subpopulations of septic patients (i.e. oncological patients[37]).

This study has several limitations. First of all, our study suffered from the absence of a multivariate analysis in the included studies, likewise the meta-analysis explored the association between LVDD and mortality in the same target population.[11 12] We were unable to perform a combined analysis of e′ and E/e′ as values were provided separately in all of the studies. Another limitation is the difficulty to diagnose LVDD in the ICU according to the recent guidelines,[13] and we must acknowledge that it is not possible to determine the influence of age and comorbidities on LV diastolic function. Our analyses are not adjusted for the confounding effect of other haemodynamic factors such as the use of inotropes/vasopressors and the volume of fluid resuscitation, as TDI assessment was not systematically reported according to such variables. In addition, no study provided a sub-analysis of data according to mechanical ventilation; a variable likely to influence myocardial relaxation and transmitral flow, especially in case of high intra-thoracic pressure. Furthermore, none of the studies differentiated patients with pulmonary sepsis from those with extra-pulmonary cause of sepsis.

Another limitation is that the observational studies included in the analyses do not determine LV diastolic function before the development of severe sepsis or septic shock. Therefore, although some evidence suggests worsening TDI values with the progression of sepsis,[40] optimal studies should include echocardiographic data prior to the onset of septic disease. We do not fully understand whether it is the direct toxic effect of sepsis on the myocardium causing the problem, or whether it is the compensatory pathophysiological alterations, or the effect of treatments on previously impaired myocardial relaxation. Timing of echocardiographic examination differed among studies (Table 2) and this may further increase the variability of our findings. We tried to account for this variability conducting a secondary analysis excluding four studies conducting a very early assessment[28 40 45] or a late evaluation.[43] This analysis did not alter the results of the primary outcomes. It is worth mentioning that four of the 31 sensitivity analyses conducted with 'leaving-one-out' at time approach showed a change of the primary results (lower e′ values showed only a trend towards increased mortality). We believe that in one case the reason is a lower statistical power of the analysis (exclusion of the largest study with a decrease of over 260 patients).[34] The other three studies[33 37 40] were smaller (47–72 patients) and we do not have a precise argument for the loss of significance in these analyses ($P=0.05$–0.06). However, as the remaining 26 sensitivity analyses and all of the secondary analyses too did not show any changes, we believe our results remain valid. Nonetheless, larger studies focused directly on echocardiographic variables and providing both septal, lateral and average TDI values would be valuable. Finally, we used mortality at the longest follow-up reported to aid quantitative analysis. There is a wide variation in the length of longest follow-up reported among the different studies: ICU,[31–33 37] 30 day,[38] in-hospital[29 34 35 41 43 45] and 90 day mortality.[30 42]

Conclusions

In patients with severe sepsis or septic shock, both lower e′ and higher E/e′ ratio showed a strong association with mortality. The values measured at the lateral mitral annulus seem to have a stronger association with outcome when compared with septal values, but the reasons for this are not clear and this finding needs to be further elucidated by prospective well-conducted studies. This study adds relevance to the growing evidence of adverse prognosis in patients with diastolic dysfunction.

Authors' contributions

All authors meet all four conditions to comply with ICMJE recommendations.

Study conception, systematic search, manual search, data retrieval, assessment of risk of bias, analysis, draft of manuscript and revision according to other authors' suggestions, final approval of the version to be published, submission: F.S.
Systematic search, manual search, data retrieval, assessment of risk of bias, analysis, critically revising the manuscript, final approval of the version to be published: C.C.
Manual search, data retrieval, assessment of risk of bias, analysis, final approval of the version to be published: A.A.
Manual search, provided supplementary data, interpretation of the data, critically revising the manuscript, final approval of the version to be published: G.L.
Manual search, interpretation of the data, critically revising the manuscript, final approval of the version to be published: A.V.-B.
Manual search, data retrieval, analysis, interpretation of the data, critically revising the manuscript, final approval of the version to be published: M.C.
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Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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Declaration of interest

The authors declare they have no conflict of interest with regards to the present work.

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