Perioperative Diastolic Dysfunction in Patients Undergoing Noncardiac Surgery Is an Independent Risk Factor for Cardiovascular Events

A Systematic Review and Meta-analysis

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ABSTRACT

Background: The prognostic value of perioperative diastolic dysfunction (PDD) in patients undergoing noncardiac surgery remains uncertain, and the current guidelines do not recognize PDD as a perioperative risk factor. This systematic review aimed to investigate whether existing evidence supports PDD as an independent predictor of adverse events after noncardiac surgery.

Methods: Ovid MEDLINE, PubMed, EMBASE, the Cochrane Library, and Google search engine were searched for English-language citations in April 2015 investigating PDD as a risk factor for perioperative adverse events in adult patients undergoing noncardiac surgery. Two reviewers independently assessed the study risk of bias. Extracted data were verified. Random-effects model was used for meta-analysis, and reviewers' certainty was graded.

Results: Seventeen studies met eligibility criteria; however, 13 contributed to evidence synthesis. The entire body of evidence addressing the research question was based on a total of 3,876 patients. PDD was significantly associated with pulmonary edema/congestive heart failure (odds ratio [OR], 3.90; 95% CI, 2.23 to 6.83; 3 studies; 996 patients), myocardial infarction (OR, 1.74; 95% CI, 1.14 to 2.67; 3 studies; 717 patients), and the composite outcome of major adverse cardiovascular events (OR, 2.03; 95% CI, 1.24 to 3.32; 4 studies; 1,814 patients). Evidence addressing other outcomes had low statistical power, but higher long-term cardiovascular mortality was observed in patients undergoing open vascular repair (OR, 3.00; 95% CI, 1.50 to 6.00). Reviewers' overall certainty of the evidence was moderate.

Conclusion: Evidence of moderate certainty indicates that PDD is an independent risk factor for adverse cardiovascular outcomes after noncardiac surgery. **(Anesthesiology 2016; 125:72-91)**

WORLDWIDE about 200 million patients undergo noncardiac surgery annually.[1,2] Of these, more than 1 million die within 30 days and 20 million experience major adverse events.[2,3] Preoperative risk prediction aims to influence clinical decision and resource planning to avoid or reduce perioperative mortality and morbidity by identifying patients for whom benefits of surgery will outweigh procedure-related harms. Recommended by American College of Cardiology/American Heart Association (ACC/AHA) guidelines, the revised cardiac risk index is a widely used risk prediction tool to stratify candidates for noncardiac surgery.[4–6] Limitations of the tool have been noted for specific surgical populations, such as patients undergoing lung resection or vascular surgery.[7,8] Modifications of the tool have been proposed to account for changes in clinical practice and subsequent revisions in the definitions of adverse events.[9,10] After accounting for predictors that are already included in a

What We Already Know about This Topic

- Cardiac morbidity and mortality remain a major source of adverse events in noncardiac surgery
- Cardiac diastolic dysfunction is an increasingly recognized form of ventricular dysfunction with high prevalence and association with morbidity
- The relationship between perioperative diastolic dysfunction and perioperative cardiac risk in noncardiac surgery is not well understood

What This Article Tells Us That Is New

- The authors have performed a random-effects meta-analysis that shows supportive evidence for perioperative diastolic dysfunction as an independent risk factor for adverse cardiovascular events after noncardiac surgery
- The work supports the importance of increased awareness of perioperative diastolic dysfunction when considering the cardiac risk factors for noncardiac surgery

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risk prediction model, factors that are independently associated with adverse perioperative outcomes are good candidates for model improvement studies.

One such candidate predictor could be diastolic dysfunction. Diastolic dysfunction is characterized by an abnormal relaxation of the ventricles, resulting in high ventricular filling pressure.[11] Diastolic dysfunction usually precedes systolic dysfunction.[12] The prevalence of diastolic dysfunction in the community is estimated to be 28% in the population 60 yr or older.[13] Kuznetsova *et al.*[14] have previously shown that low early diastolic mitral annulus velocity measured by tissue Doppler imaging was an independent predictor (above and beyond the traditional cardiovascular risk factors) of fatal and nonfatal cardiovascular events in the general population. Onset of the dysfunction is asymptomatic and preclinical, progressing over time to symptomatic diastolic heart failure. With aging population demographics, interest in preclinical diastolic dysfunction as a risk factor for cardiovascular outcomes is attracting more attention. While diastolic dysfunction may affect both ventricles, it is mostly the left ventricular diastolic dysfunction that is reported in association with adverse cardiovascular outcomes. In this review, left ventricular diastolic dysfunction will be referred to as perioperative diastolic dysfunction (PDD).

Echocardiography is the imaging modality and the accepted standard used to determine the presence of diastolic dysfunction in clinical practice.[15] The severity of diastolic dysfunction is classified as mild or impaired relaxation (grade I), moderate or pseudonormal (grade II), and severe or restrictive (grade III) based on echocardiographic findings. The guidelines recommend a set of echocardiographic measurements[15]: the mitral inflow parameters (E/A ratio, isovolumic relaxation time, and deceleration time), tissue Doppler of the mitral annulus (é), pulmonary venous flow (S, D, and A waves), transmitral propagation velocity (Vp), and E/é ratio. The E/é ratio is being widely adopted in clinical research.

Perioperative diastolic dysfunction has been found to be significantly associated with in-hospital mortality, major adverse cardiovascular events (MACE), difficult weaning from cardiopulmonary bypass, and the need for more frequent inotropic/vasoactive pharmacologic support in patients undergoing cardiac surgery.[16–18] The relationship between PDD and adverse outcomes after noncardiac surgery, however, is less well understood. The recent ACC/AHA Guidelines on Perioperative Cardiovascular Evaluation for Non-Cardiac Surgery consider heart failure (diastolic or systolic) as a major risk factor without reference to PDD.[5,6]

We undertook a systematic review of the literature to investigate whether existing evidence supports PDD as an independent predictor of adverse health outcomes in patients undergoing noncardiac surgery. The research question articulated in our *a priori* protocol was the following: Is perioperative left ventricular diastolic dysfunction an independent predictor of adverse health outcomes within 30 days of noncardiac surgery?

Materials and Methods

We followed a prespecified systematic review protocol. Our review was prospectively registered (Centre for Reviews and Dissemination 42015020173) with the International Prospective Register of Systematic Reviews (PROSPERO).

Data Sources

A systematic search was conducted for studies published from 1946 to April 2015 by searching Ovid MEDLINE, PubMed, EMBASE, and the Cochrane Library. Additional search was conducted using the Google search engine. Keywords and medical subject headings related to diastolic dysfunction, perioperative/intraoperative period, and noncardiac surgery were used. The search results were limited to English language and human studies. The full search strategy is provided in appendix 1.

Study Selection

One reviewer (A.F. or M.A.) screened titles and abstracts for potential relevance, and a second reviewer (H.Y.) verified exclusions at this level. Two independent reviewers (A.F. and H.Y.) assessed the full publication of potentially relevant studies, and discrepancies were resolved by consensus.

We included analytic observational studies on adult patients undergoing noncardiac surgery, comparing echocardiographically established PDD with normal left ventricular diastolic function, lower grade PDD, or both. We accepted all investigator-defined PDD. Eligibility was also restricted to studies that were reported in the English language. We excluded studies that exclusively included patients with symptomatic diastolic dysfunction or congestive heart failure (CHF), patients with low ejection fraction, or patients undergoing cardiac procedures. We also excluded studies that used biomarker proxies of diastolic dysfunction without echocardiographic confirmation to minimize specificity concerns.

Data Extraction and Critical Appraisal

After piloting data extraction forms, a single reviewer (M.T.A.) extracted general study characteristics, including funding source, sample size, study design, eligibility criteria, description of population, exposure definition and measurement details, outcome definition, time point/follow-up duration, measurement tool or scale, cutoffs employed, level of care, type of surgery and anesthesia protocol, quantitative outcome data, statistical test used, and covariate adjustment. Another reviewer (A.F.) independently verified outcome data.

Two reviewers (M.T.A. and A.F.) judged study applicability and risk of bias. For each outcome of interest, we assessed study risk of bias using the Quality In Prognosis Studies tool that covers six domains, namely, study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting.[19] Applicability was based on population description,

exposure ascertainment (*i.e.*, definition of PDD, echo parameter criteria, and imaging modality), setting, outcome definition, level of care, and anesthesia and surgery protocols. To assess clinical applicability of investigator-defined PDD, we examined whether the characterization of PDD was based on at least one of the following echocardiographic parameters either as individual measurements or in combination with other diastolic parameters.

- Mitral E/A ratio (m/s) = early diastolic filling velocity (E-wave) divided by atrial contraction filling velocity (A-wave)
- Transmitral flow propagation velocity (Vp)
- E/é ratio: the ratio of early diastole E wave mitral inflow to annular velocity é

The overall study risk of bias was categorized as high, moderate, or low. Applicability assessment was rated as no concern and major or minor concerns. To assess confounding in included studies, we considered age, sex, weight, history of cardiovascular disease, diabetes mellitus, renal dysfunction, hypertension, type of surgery, and type of anesthesia as potential confounders.

We employed the directed acyclic graph approach to map the causal relationship of potential confounders with the exposure (*i.e.*, PDD) and outcomes of interest.[20,21] This approach is helpful in understanding the structure of biasing pathways. According to the structural theory of epidemiologic bias, a confounder is a "common cause" of both the exposure (*i.e.*, perioperative left ventricular diastolic dysfunction in this case) and the outcome (*e.g.*, cardiovascular death). Confounding bias is controlled in the design of a study (*e.g.*, by matching on a confounder variable) or in its analyses (*e.g.*, statistical adjustment). A "common effect" of exposure and outcome should not be adjusted for in the design or analysis because this will lead to selection bias (for details, readers are referred to the article by Hernán *et al.*[20]).

As such, we depicted the structure of causal relationships between a covariate, the exposure (left ventricular diastolic dysfunction), and the outcomes to identify potential confounders and assess whether studies adequately controlled confounding bias (appendix 2). The depicted relationships were informed by our understanding of the pathophysiology of diastolic dysfunction. We used online DAGitty software for this purpose.[21] The DAGitty software computed the following "minimal sufficient adjustment" sets that studies should optimally control for in the study design or analysis when investigating an unconfounded association between PDD and adverse postsurgical outcomes:

- Cardiovascular disease, diabetes mellitus, hypertension, type of anesthesia, and type of surgery, or
- Cardiovascular disease, renal dysfunction, type of anesthesia, and type of surgery

Because age and history of chronic diseases are commonly employed proxies for the duration of disease exposure, we examined whether studies adequately controlled for age, history of aforementioned chronic diseases, type of surgery, and anesthesia protocol.

Specifically for studies comparing higher with lower grade PDD, the use of postoperative angiotensin receptor blocker or angiotensin-converting enzyme inhibitor was considered an additional important confounder. For studies that were not conducted exclusively in patients with normal ejection fraction, we also assessed for adequacy of control for this variable in either the design or the analysis of studies while assessing risk of bias.

Data Synthesis and Analysis

The prespecified 30-day outcomes were all-cause mortality, cardiovascular death, pulmonary edema or congestive cardiac failure, length of hospital stay, MACE, myocardial ischemia or infarction, and arrhythmia requiring treatment. Data were quantitatively pooled unless between-study heterogeneity (I^2 > 50%) could be explained by study-level clinical or methodologic covariates. Data were pooled in Review Manager 5.3 using random-effects generic inverse variance or Mantel–Haenszel method (Review Manager [RevMan] [Computer Program]; Version 5.3; Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). When both adjusted and crude estimates of association were reported, adjusted estimates were selected for meta-analyses. When applicable, we had planned to undertake sensitivity analyses by study risk of bias. We had also planned subgroup analyses for the various grades of PDD, baseline cardiac preoperative risk scores, or other important study-level clinical covariates identified *post hoc*. Because of the limited number of data-contributing studies, we could not statistically test for publication bias.

Assessment of Reviewers' Certainty in Estimates of Association

Two reviewers (M.T.A. and A.F.) used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to rate their certainty (or confidence) in estimates of prognostic association using the four tier levels of high, moderate, low, or very low.[22,23] For prognostic inference, sound cohort, case-cohort, and nested case-control studies provide the highest quality of evidence.[22,24] Reviewers' certainty in evidence is downgraded when there are important limitations in the validity and generalizability of studies, inconsistency between them, lack of statistical power in the data, or concerns about publication bias. Certain factors (*e.g.*, dose–response relationship and large difference in absolute risk) increase our certainty in estimates. We did not formally grade the certainty of estimates of association that were bounded by wide CIs, precluding meaningful conclusions.

Results

A total of 859 records were identified and screened for eligibility. Seventeen studies met the inclusion criteria for the review (fig. 1). Of those, four studies did not contribute to evidence

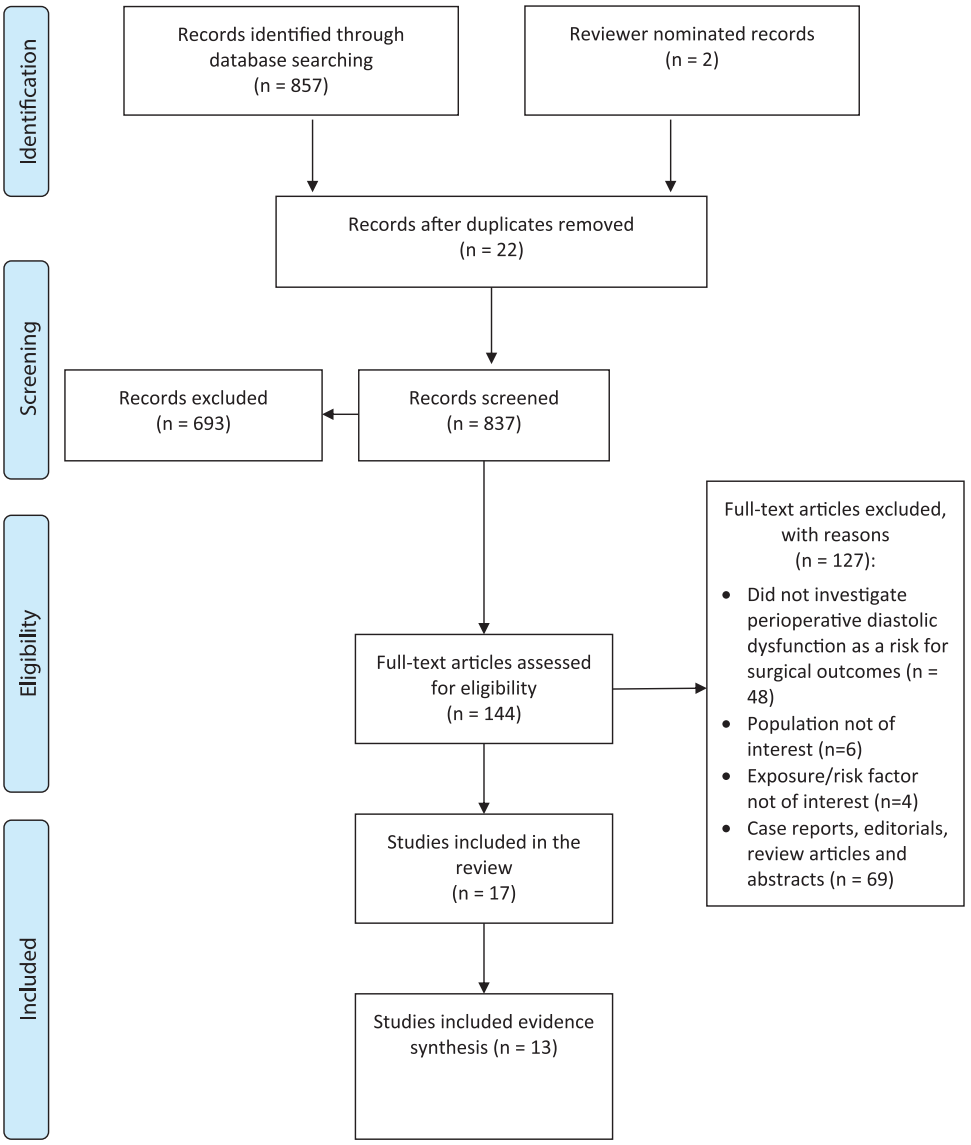

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow systematic review diagram.

synthesis either because data for outcomes of interest were not reported or because classification of exposure and controls was unclear.[25–28] The remaining 13 studies contributing evidence were of diverse methodologic and clinical characteristics (table 1). Design of the included studies was observational prospective cohort (N = 6), retrospective chart review (N = 6), and case-control (N = 1). PDD was defined as per E/A ratio, E/é ratio, or both parameters with or without consideration of deceleration time. One study, however, defined PDD with transmitral flow propagation velocity (Vp).[34] There was heterogeneity in ratio cutoffs for the E/A (0.75, 0.8, and 1.0) and E/é (8, 10, and 15) parameters across the studies with most studies comparing mixed or specific grades of PDD with normal diastolic function (N = 9).[30,31,34,36–41] Four studies compared higher (*i.e.*, moderate or severe) grade PDD with the composite of normal diastolic function and lower (*i.e.*, various permutations of mild or moderate) grade PDD.[29,32,33,35]

Mean age of patients across the 13 studies ranged from 45 to 72 yr. Type of anesthesia administered to patients was not reported in six studies, but the rest reported using general anesthesia protocols.[29,33,36–38,40] Of note, Flu *et al.*[30] employed general anesthesia for all open vascular repairs and 35% of endovascular surgeries.

The entire body of evidence addressing the research question was based on a total of 3,876 patients. Because of frequent nonreporting of symptomatic/asymptomatic status of patients or unclear accounting for symptoms of heart failure in statistical analyses across the studies, we documented our corresponding generalizability concerns under assessment of external validity (table 1).

Risk of Bias in Included Studies

Except for the composite outcome of postoperative adverse events reported in the study by Matyal *et al.*,[34] outcome data

Table 1. Characteristics of Included Studies

Author	Study Design	Sample Size	Patient Population	PDD (Exposure) Definition	Comparison	Region	Funding	External Validity
Ghanami *et al.*[29]	Retrospective cohort	76	Patients undergoing open renal artery revascularization for atherosclerotic disease (unclear whether patients were in preclinical PDD; 21% had EF < 50% (which was not associated with diastolic function) and 9% had history of CHF)	Preoperative; TTE; E/A cutoff was ≤ 0.75 and E/é < 10 (E/é values were used when E/A classification differed)	Moderate-to-severe PDD *vs.* none/mild PDD	North America	NR	Minor concerns: unclear about asymptomatic status of patients
Flu *et al.*[30]	Prospective cohort	Open vascular surgery = 449; endovascular surgery = 259	Patients undergoing *elective open* or *endovascular* lower extremity artery, carotid artery, or abdominal aorta repair (subgroup with no symptoms of heart failure and preserved EF)	Preoperative; TTE; E/A ratio < 0.8 or > 2; pseudonormal PDD = E/A 0.8–2 and abnormal pulmonary vein flow (S/D < 1)	PDD *vs.* normal LV diastolic function	Europe	Lijf en leven foundation	No concerns: asymptomatic PDD
Fayad *et al.*[31]	Prospective cohort	9	Patients with normal LV systolic and diastolic function (E/A > 1) undergoing thoracoabdominal aortic aneurysm repair. No symptoms of heart failure. PDD was observed intraoperatively in some patients due to clamping of aorta	Intraoperative; TEE; E/A ratio < 1	Mild/pseudonormal PDD *vs.* normal LV diastolic function	North America	NR	Major concerns: a substantial proportion of the PDD may be iatrogenic due to aortic cross-clamping with return to normal function after removal of the clamp
Cho *et al.*[32]	Prospective cohort	692	Patients aged > 60 yr who were indicated for low- or intermediate-risk nonemergent, noncardiac surgery; 4% had CHF and 82% underwent intermediate-risk surgery. 92% had preserved LV EF. Data analysis of interest is restricted to patients with preserved LV EF.	Preoperative; TTE; E/é ratio > 15	Grade III *vs.* normal LV diastolic function or grade I/II PDD	Asia Pacific	NR	Minor concerns: study from Asia Pacific region. Unclear whether patients had no symptoms of heart failure at baseline
Saito *et al.*[33]	Retrospective cohort	200	Consecutive patients with cardiovascular diseases who had undergone tissue Doppler echocardiography before noncardiac surgery; 5% had congestive heart failure; 82% of patients had a preserved LV EF of > 50%	Preoperative; TTE; E/é ratio > 15	Grade III *vs.* normal LV diastolic function or grade I/II PDD	Asia Pacific	NR	Minor concerns: study from Asia Pacific region. Unclear whether patients had no symptoms of heart failure at baseline.

(*Continued*)

Table 1. (Continued)

Author	Study Design	Sample Size	Patient Population	PDD (Exposure) Definition	Comparison	Region	Funding	External Validity
Matyal *et al.*[34]	Prospective cohort	214	Consecutive patients undergoing elective aortic or peripheral vascular surgery under general anesthesia; 14% had CHF, majority were with preserved EF (≥ 40)	Intraoperative; TEE; transmitral flow propagation velocity (Vp) < 0.45 m/s	PDD *vs.* normal LV diastolic function	North America	Not funded	Minor concerns: estimates may not represent asymptomatic/preclinical diastolic dysfunction. A proportion of the PDD may be iatrogenic due to aortic cross-clamping with return to normal function after removal of the clamp. Major concerns for the outcome "length of hospital stay" because reported analysis included 36% of patients with PDD who also had systolic dysfunction.
Higashi *et al.*[35]	Case-control (unclear whether all patients were asymptomatic for PDD)	190	Adult patients who underwent living-donor renal transplantation in a hospital in Japan (excluded patients with EF < 50%)	Preoperative; TTE; E/é ratio < 8 and ≥15; E/A ratio (cutoff not reported)	Higher *vs.* lower E/é	Asia Pacific	Departmental funding	Minor concerns: unclear whether asymptomatic preoperative PDD; study in Asian population
Anile *et al.*[36]	Prospective cohort	72	Adult with no previous history of atrial fibrillation undergoing lung parenchymal resection surgery	Preoperative; TTE; E/A ratio (cutoff NR)	Mild *vs.* normal LV diastolic function	Europe	NR	Major concerns: outcome is not all treatment requiring arrhythmia but rather pharmacologically treated atrial fibrillation
Mittal *et al.*[37]	Retrospective cohort	970	Adult patients undergoing liver transplantation whose previous preoperative TEE assessments were available	Preoperative; TTE; E/A and E/é ratio: normal, 2.3 ± 0.6 and < 10; grade I, ≤ 1.0 and < 10; grade II, 2.3 ± 0.6 and > 10; grade III, > 1.5 and > 10	Mild, moderate, and severe *vs.* normal LV diastolic function	North America	NR	Major concerns: liver transplantation surgery is unique because after surgery hemodynamics would have likely changed substantially from preoperative states and altered diastolic function, which was evaluated presurgery. Also, it is unclear as to what proportion of patients had low EF and whether patients were asymptomatic for PDD.
Nojiri *et al.*[38]	Prospective cohort	126	Consecutive non–small-cell lung cancer patients undergoing elective pulmonary resection at a tertiary care hospital in Japan	Preoperative; TTE; E/é > 8	PDD *vs.* normal LV diastolic function	Asia Pacific	NR	Minor concerns: unclear as to what proportion of patients had low EF. Also unclear whether patients were asymptomatic for PDD presurgery. Further, the relevant outcome is not exclusively patients requiring treatment for atrial fibrillation, but majority (> 80%) required pharmacologic treatment.

(*Continued*)

Table 1. (Continued)

Author	Study Design	Sample Size	Patient Population	PDD (Exposure) Definition	Comparison	Region	Funding	External Validity
Raevens *et al.*[39]	Retrospective cohort	173	Adult patients undergoing liver transplantation	Preoperative; TTE; E/A < 1 or DT > 200 ms	PDD *vs.* normal LV diastolic function	Europe	NR	Major concerns: liver transplantation surgery is unique because after surgery hemodynamics would have likely changed substantially from preoperative states and altered diastolic function, which was evaluated presurgery. Also, unclear whether patients were asymptomatic for PDD.
Shounak *et al.*[40]	Retrospective cohort	140	Patients with liver cirrhosis undergoing TIPS and abdominal surgery including liver transplantation who had documented echocardiographic data. More than 50% of patients had liver transplant.	Preoperative; TTE; presence of two of the following: DT > 250 ms, E/A ratio < 1, medial Á> É, or peak flow systole/diastole ratio > 1.5 (grade I) & DT < 160 ms, E/A > 1, medial E/é > 15, peak flow systole/diastole ratio < 0.3, or medial É < 7 cm/s (grade II or III)	PDD (mostly grade I) *vs.* normal LV diastolic function	North America	NR	Major concerns: majority of patients underwent liver transplantation surgery and TIPS. These are unique procedures because after surgery hemodynamics would have likely changed substantially from preoperative states and altered diastolic function, which was evaluated presurgery.
Xu *et al.*[41]	Retrospective cohort	306	Adult patients undergoing cadaveric orthotopic liver transplantation in a local hospital in China	Preoperative; approach NR; for age < 50 yr, E/A < 1 and DT > 220 ms and E/é > 8; for age > 50 yr, E/A < 0.5 and DT > 280 ms and E/é > 8	PDD *vs.* normal LV diastolic function	Asia Pacific	Science and Technology Commission of Shanghai Municipality	Major concerns: liver transplantation surgery is unique because after surgery hemodynamics would have likely changed substantially from preoperative states and altered diastolic function, which was evaluated presurgery. Furthermore, unclear description of population in terms of baseline cardiac status and EF.
Bitoh *et al.*[25]	Not included in evidence synthesis because this study on eight patients undergoing infrarenal abdominal aortic aneurysm repair does not clearly classify exposure and control levels of PDD parameters for the outcome pulmonary edema that occurred in two patients							
Ai *et al.*[26]	A case-control study. Not included in evidence synthesis because it is unclear whether patients were free of manifestation of heart failure. Also, no data of interest are reported. Atrial fibrillation specifically is not an outcome of interest							
Mahmood *et al.*[27]	No outcomes data of interest were reported							
Shillcutt *et al.*[28]	No outcomes data of interest were reported							

CHF = congestive heart failure; DT = deceleration time; EF = ejection fraction; LV = left ventricle; NR = not reported; PDD = perioperative diastolic dysfunction; S/D = systolic and diastolic pulmonary vein flow velocity ratio; TEE = transesophageal echocardiography; TIPS = transjugular intrahepatic portosystemic shunt; TTE = transthoracic echocardiogram.

were judged to be at significant risk of bias across all studies (table 2). In general, the risk of bias concerns were frequently about selection of participants and residual confounding, although studies were also at risk of bias for various other reasons such as subjective, nonblinded classification of diastolic dysfunction or outcome ascertainment and unclear reporting of patient attrition and handling of missing data.

All-cause Mortality

In total, seven studies reported this outcome assessed at variable short- and long-term durations after surgery.[29,30,34,37,39–41] We meta-analyzed data from the three studies reporting 30-day or in-hospital mortality, which yielded a nonsignificant odds ratio (OR) with wide CI for PDD (mixed grades) *versus* normal diastolic function (OR, 1.10; 95% CI, 0.62 to 1.94). Adding the retrospective cohort study by Raevens *et al,*[39] which reported short-term mortality after 3 months of liver transplant surgery, did not change the pooled estimate on early mortality after surgery (fig. 2).

As an exploratory meta-analysis to harness the cumulative power of the evidence base, we also pooled mortality data irrespective of observational study designs, surgical diversity, and outcome measurement time points (range: in-hospital stay to several years postsurgery). Irrespective of severity, PDD was not significantly associated with combined short- and long-term all-cause mortality, but the body of evidence was underpowered to detect a difference (fig. 3). Whether patients had vascular or hepatic surgeries did not yield any statistically significant subgroup differences. Restricting the meta-analysis to studies specifically comparing moderate-to-severe PDD with no or mild PDD also yielded imprecise pooled estimate, but association with higher mortality could not be ruled out (fig. 4).

Cardiovascular Death

The 30-day cardiovascular mortality was reported in the study by Flu *et al*[30] on 708 patients undergoing elective open or endovascular repair. There were 11 cardiovascular deaths within 30 days (OR, 2.01; 95% CI, 0.61 to 6.67). For a mean follow-up of 2.2 yr, significantly higher (adjusted) odds of cardiovascular death with PDD were observed in the subgroup of patients undergoing open vascular repair (OR, 3.00; 95% CI, 1.50 to 6.00) as opposed to elective endovascular procedures.

Pulmonary Edema/CHF

One case-control and two prospective cohort studies reported this outcome during the period of hospitalization after surgery[32,34,35] (table 2). A significant association (OR, 3.90; 95% CI, 2.23 to 6.83) between PDD and CHF/pulmonary edema was observed (fig. 5). The study by Cho *et al.*[32] reported estimates of association separately for PDD defined by E/é and E/A ratios. Pooled estimate did not change in sensitivity meta-analyses guided by different definitions of PDD.

Studies were clinically diverse in their echocardiographic approaches, parameters defining PDD, surgery types, mean age of participants, and how pulmonary edema was defined—however, all studies included radiologic evidence in their definition. Diversity was also noted because studies either compared PDD (irrespective of grade) with normal diastolic function or compared moderate to severe PDD with combined mild PDD and normal diastolic function.

Length of Hospital Stay

Three studies reported this outcome in a total of 660 patients undergoing vascular, abdominal, or hepatic surgical procedures[34,40,41] (tables 1 and 2). PDD definitions and the analysis of the length of hospital stay data were inconsistent, so meta-analysis was not possible. Matyal *et al.*[34] found significantly longer hospitalization in patients with PDD irrespective of their ejection fraction (median of 7 *vs.* 5 days). Shounak *et al.*[40] found that a greater proportion of patients with PDD undergoing abdominal surgery were hospitalized longer term, but the findings were not statistically significant. Xu *et al.*,[41] on the other hand, found no association between length of stay and PDD in patients undergoing orthotopic liver transplantation.

Major Adverse Cardiovascular Events

Three studies reported 30-day MACE outcomes data.[30,32,33] MACE was variably defined by investigators, but data were far too inadequate to undertake any meta-regression or subgroup analyses sensitive to MACE definitions. All MACE definitions included acute coronary events and mortality. Another study by Matyal *et al.*[34] reported the composite of in-hospital postsurgical adverse events, which we considered a reasonable approximation of 30-day MACE. Observed statistical heterogeneity was not explained by study risk of bias, type of surgery, or definition of PDD. Furthermore, notable overlap of CIs was observed. From a clinical decision-making perspective, the consistency in the direction of estimates of association despite the observed clinical and methodologic diversity across the studies compelled a formal meta-analysis. Pooled estimate of association (OR, 2.03; 95% CI, 1.24 to 3.32) demonstrated a significant risk of MACE with PDD (fig. 6 and table 3). Risk estimate remained unchanged when we excluded the study by Matyal *et al*[34] from the meta-analysis.

Myocardial Ischemia or Infarction

Three studies on patients undergoing various vascular procedures were included in this analysis. PDD-defining parameters and cutoffs were heterogeneous. Follow-up duration ranged from 48 h postsurgery to the entire period of hospitalization. Pooled estimate revealed higher odds (OR, 1.74; 95% CI, 1.14 to 2.67) of myocardial ischemia or infarction with PDD in the short-term period after surgery (fig. 7).

Table 2. Included Study Risk of Bias

Author	Outcome Domain	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Confounding	Analysis and Reporting	Overall Risk of Bias	Justification for Overall Risk of Bias
Ghanami *et al.*[29]	All-cause mortality	High	Moderate	Moderate	Low	High	Moderate	High	Longer-term, time-varying confounders (*e.g.*, treatment adherence, other subsequent surgeries, illness, hospitalization, surgical-site infection, comedications) were not measured or accounted for this outcome besides high risk of selection bias because of nonrandom sampling.
Flu *et al.*[30] (open vascular or endovascular surgery)	All-cause mortality, cardiovascular mortality and myocardial infarction/ischemia at 30 days	Low	Low	Moderate	Low	High	Low	High	Unadjusted estimates
Flu *et al.*[30] (open vascular surgery)	MACE	Low	Low	Moderate	Low	Moderate	Low	Moderate	Unclear about blinded assessment of PDD. At some risk of over adjustment of baseline prognostic factors and nonadjustment for specific surgery types
	Cardiovascular death	Low	Low	Moderate	Moderate	High	Low	High	Nonadjustment for important post-surgery long-term time-varying confounders; mortality data were obtained from municipal registries
	All-cause mortality	Low	Low	Moderate	Moderate	High	Low	High	
Flu *et al.*[30] (endovascular surgery)	MACE	Low	Low	Moderate	Low	Moderate	Low	Moderate	Unclear about blinded assessment of PDD. At some risk of over adjustment of baseline prognostic factors and nonadjustment for specific surgery types
	Cardiovascular death	Low	Low	Moderate	Moderate	High	Low	High	Nonadjustment for important post-surgery long-term time-varying confounders; mortality data were obtained from municipal registries
	All-cause mortality	Low	Low	Moderate	Moderate	High	Low	High	
Fayad *et al.*[31]	Myocardial infarction/ischemia	Low	Low	Moderate	Low	High	High	High	Unadjusted estimates can be calculated, high risk of confounding by comedications. E/A cutoff < 1

(*Continued*)

Table 2. (Continued)

Author	Outcome Domain	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Confounding	Analysis and Reporting	Overall Risk of Bias	Justification for Overall Risk of Bias
Cho *et al.*[32] (PDD as per E/é ratio)	CHF/pulmonary edema	Moderate	Moderate	Moderate	Moderate	High	Moderate	High	Major concerns about residual confounding (unclear what variables were included in stepwise logistic regression analysis. Certainly did not adjust for type of anesthesia, surgery, and use of postoperative angiotensin receptor blocker or angiotensin-converting enzyme inhibitor). Subjective but blinded assessment of pulmonary edema. Combined normal, grade I and II PDD into one control group. Also concerns about random sampling that was not described.
	MACE	Moderate	Moderate	Moderate	Moderate	High	Moderate	High	
Cho *et al.*[32] (PDD as per E/A ratio)	CHF/pulmonary edema	Moderate	Moderate	Moderate	Moderate	High	Moderate	High	
	MACE	Moderate	Moderate	Moderate	Moderate	High	Moderate	High	
Saito *et al.*[33]	MACE	High	Moderate	High	High	Moderate	High	High	Major retrospective design limitations including nonrandom sampling. Also, limitations in classification of exposure cutoff and MACE and reporting of adjustment for important confounders for the estimate of association. Furthermore, retrospective, nonblinded determination of echo parameters.
Matyal *et al.*[34]	Postoperative adverse outcomes (composite)	Low	Low	Low	Low	Low	Low	Low	NA
	LOHS	Low	Low	Low	Low	High	High	High	Unadjusted estimate of effect
	CHF/pulmonary edema	Low	Low	Low	Moderate	High	High	High	Unadjusted estimates; nonblinded chest radiograph interpretation of pulmonary edema
	Arrhythmia requiring treatment	Low	Low	Low	Low	High	High	High	Only unadjusted odds can be estimated
	Myocardial infarction/ischemia	Low	Low	Low	Low	High	High	High	Only unadjusted odds can be estimated
	All-cause mortality	Low	Low	Low	Low	High	High	High	Only unadjusted odds can be estimated
Higashi *et al.*[35]	CHF/pulmonary edema	Moderate	Moderate	Moderate	Moderate	High	Moderate	High	Case-control design, concerns about exposure and outcome ascertainment bias and important residual confounding, unclear description of cutoffs for higher/lower E/é ratio

(*Continued*)

Table 2. (Continued)

Author	Outcome Domain	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Confounding	Analysis and Reporting	Overall Risk of Bias	Justification for Overall Risk of Bias
	CHF/pulmonary edema	Moderate	Moderate	Moderate	Moderate	High	Moderate	High	Case-control design, concerns about what the source population was, exposure and outcome ascertainment bias, important residual confounding, and unclear description of cutoffs for higher/lower E/é ratio
Anile *et al.*[36]	Atrial fibrillation requiring pharmacologic treatment	High	Low	High	Low	High	Moderate	High	Inadequate description of the sampling frame, unclear prognostic factor definition, exclusion of patients with minor lung resection and inadequate adjustment for confounding
Mittal *et al.*[37]	All-cause mortality	High	Low	Low	Low	High	Low	High	A retrospective review of patients who had previous preoperative TEE assessment—eligible patients who did not have preoperative TEE could not be included. Also, did not adjust for concomitant low ejection fraction in unknown percentage of patients.
Nojiri *et al.*[38]	Atrial fibrillation requiring pharmacologic treatment	Moderate	Low	Low	Low	High	Low	High	Concerns about residual confounding—did not adjust for ejection fraction, diabetes mellitus, and hypertension
Raevens *et al.*[39]	All-cause mortality and MACE defined as "cardiovascular complications"	High	Low	Low	Low	High	Low	High	At high risk of selection bias because echocardiographic parameters were not available for some patients who were excluded. Patients who underwent reoperation were also excluded. At risk of confounding because did not measure and adjust for key confounders.
Shounak *et al.*[40]	All-cause mortality and length of hospital stay	High	Moderate	Low	Low (moderate for length of hospital stay)	High	Low	High	At high risk of selection bias because echocardiographic parameters were not available for some patients who were excluded. At risk of confounding because did not measure and/or adjust for key confounders
Xu *et al.*[41]	All-cause mortality and length of hospital stay	High	Low	Low	Low	High	Low	High	High risk of selection bias due to retrospective design, exclusion of alcoholic cirrhosis and hemochromatosis, and high likelihood that selective patients with complete exposure and outcome data were analyzed. Baseline characteristics of the population are poorly described. Furthermore, crude-unadjusted estimates only.

CHF = congestive heart failure; LOHS = length of hospital stay; MACE = major adverse cardiac events; NA = not applicable; PDD = perioperative diastolic dysfunction; TEE = transesophageal echocardiography.

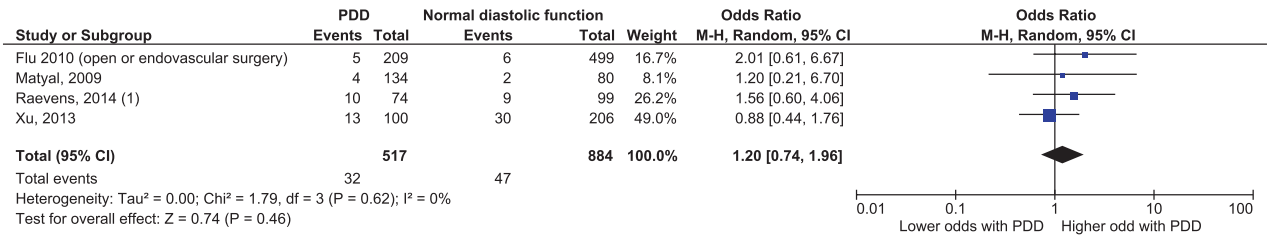

Fig. 2. Perioperative diastolic dysfunction (PDD) (mixed grades) *versus* normal diastolic function: 30-day, all-cause mortality. (1) Three-month mortality data (inclusion did not change pooled estimate). *df* = degrees of freedom; M-H = Mantel–Haenszel.

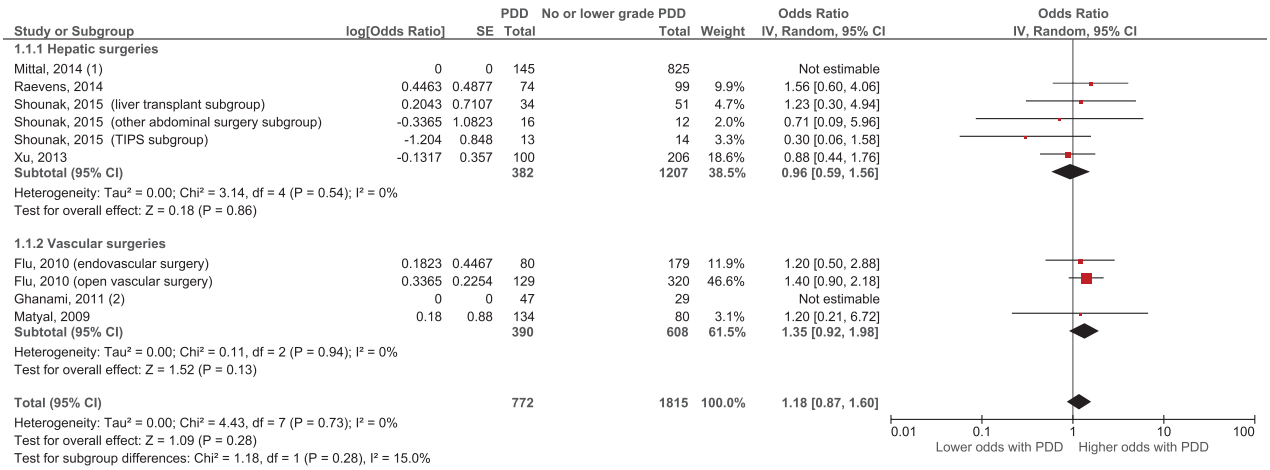

Fig. 3. Higher grade *versus* no or lower grade perioperative diastolic dysfunction (PDD): short- or long-term, all-cause mortality. (1) Mild/moderate/severe PDD *versus* no PDD (mean follow-up of 5 yr), adjusted HR = 0.93 (95% CI, 0.32 to 2.73)/1.58 (95% CI,1.04 to 2.39)/1.73 (95% CI, 1.17 to 2.53). (2) Moderate-severe PDD *versus* low-grade to no PDD (mean follow-up of 3.5 yr), adjusted HR = 5.84 (95% CI, 1.35 to 25.23). *df* = degrees of freedom; HR = hazard ratio; IV = inverse variance; SE = standard error; TIPS = transjugular intrahepatic portosystemic shunt.

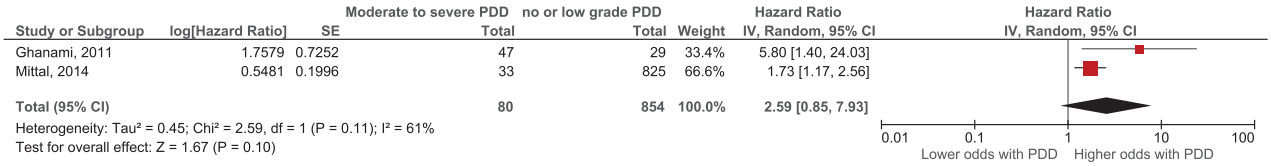

Fig. 4. Moderate-to-severe *versus* no to mild-grade perioperative diastolic dysfunction (PDD): long-term, all-cause mortality. *df* = degrees of freedom; IV = inverse variance; SE = standard error.

Arrhythmia Requiring Treatment

Crude estimate obtained from a single study on patients undergoing elective aortic or peripheral vascular surgery under general anesthesia failed to reveal any significant association between PDD and arrhythmia requiring treatment for the period of hospitalization (OR, 1.89; 95% CI, 0.66 to 5.42).[34] Given wide CI around the point estimate, findings were inconclusive.

Two other studies on patients undergoing lung surgery reported data for atrial fibrillation requiring treatment in the immediate postsurgical period.[36,38] Findings were conflicting. Both studies were at high risk of bias for various reasons (table 2). Anile *et al.*[36] found nonsignificant association with PDD, while Nojiri *et al.*[38] demonstrated a relative risk of 1.81 (95% CI, 1.36 to 2.42). To be noted, the latter included an unknown proportion of patients with low ejection fraction and did not adjust for it in their analysis.

Grading Reviewers' Certainty for Estimates of Association

For outcomes with statistically significant findings, our certainty varied from very low to moderate (table 3). Because evidence was underpowered yielding very wide CIs, an association between PDD and 30-day and longer-term all-cause mortality, 30-day cardiovascular death, length of hospital stay, and arrhythmia requiring treatment could neither be confirmed nor be refuted.

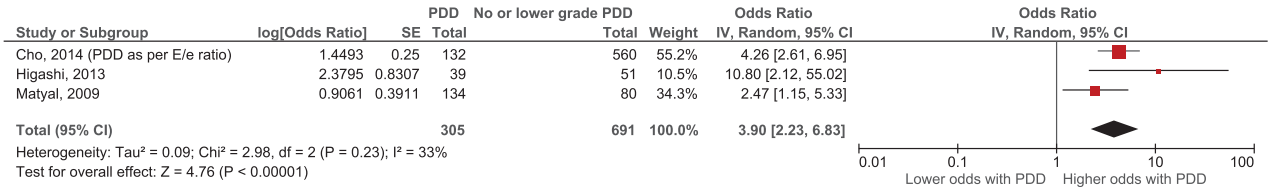

Fig. 5. Higher grade *versus* no or lower grade perioperative diastolic dysfunction (PDD): congestive heart failure or pulmonary edema (in hospital). *df* = degrees of freedom; IV = inverse variance; SE = standard error.

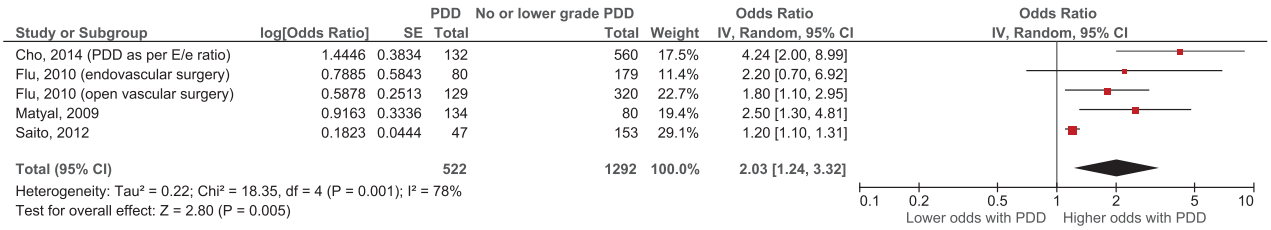

Fig. 6. Higher grade *versus* no or lower grade perioperative diastolic dysfunction (PDD): 30-day major adverse cardiovascular events. *df* = degrees of freedom; IV = inverse variance; SE = standard error.

Discussion

This is the first critical review of the association between PDD and perioperative outcomes in patients undergoing noncardiac surgery. Our systematic review and meta-analysis included more than 3,800 patients undergoing a variety of different noncardiac surgeries. We found scant evidence addressing several key outcomes for the immediate postsurgical period. However, PDD may be an independent predictor of MACE as a composite outcome as well as CHF and myocardial infarction as independent outcomes in the immediate period after surgery. Evidence also demonstrated an association between PDD and cardiovascular death in patients undergoing major surgical procedures, particularly open vascular surgeries. Furthermore, evidence in this analysis does not rule out the possibility that moderate- to severe-grade PDD may also be associated with higher all-cause mortality in patients undergoing noncardiac surgery (hazard ratio, 2.59; 95% CI, 0.85 to 7.93).

The prevalence of PDD in patients undergoing noncardiac surgery is unknown. The reported prevalence of the diastolic dysfunction in the general population, however, varies from 11.1 to 34.7%.[35,42,43] As such, with the large population of 200 million patients undergoing noncardiac surgeries annually, at least 20 to 70 million individuals may be at higher risk of MACE due to PDD. Higher prevalence of diastolic dysfunction is observed, particularly in the elderly, patients with coronary artery disease, hypertension, diabetes mellitus, cardiomyopathies, valvular disease, and a variety of other systemic diseases.[11,44–52] Preoperative identification and management of this large at-risk surgical group has the potential to improve perioperative outcomes of surgery and utilization of scarce resources.

Several limitations inherent in the body of evidence yielded very low to low certainty for most of the aforementioned outcome-specific estimates of risk as judged using the GRADE approach.[22,23] With moderate certainty, however, we can state that 47 more per 1,000 patients (95% CI, from 11 more to 99 more) will experience a MACE within 30 days of noncardiac surgery if they have PDD compared with those without diastolic dysfunction. Notwithstanding, when outcome-specific evidence is viewed *in toto*, a biologically plausible and coherent account of evidence can be immediately appreciated. If findings were spurious, the direction of association across the cardiovascular outcomes would have been randomly inconsistent and pathophysiologically incoherent. Such is clearly not the case. The higher incidence of MACE, heart failure, myocardial infarction, and cardiovascular death in noncardiac surgical patients with perioperative PDD provides evidence in keeping with the known pathophysiology of cardiovascular disease. While the observed individual estimates of association may be less certain, when viewed collectively, evidence of moderate certainty supports perioperative PDD as a risk predictor of adverse cardiovascular outcomes after noncardiac surgery.

The pathophysiology of diastolic dysfunction provides a biological rationale for an association with myocardial ischemia/infarction, pulmonary edema, and MACE. Left ventricle (LV) end-diastolic pressure is an important factor affecting the oxygen supply to the myocardium. The amount of blood flow entering the coronary circulation during diastole is the result of the pressure gradient between the epicardial coronary artery and the subendocardial segment. Elevation of the LV end-diastolic pressure, as in diastolic dysfunction patients, can reduce this gradient significantly, decreasing the coronary diastolic blood flow and subsequently decreasing myocardial perfusion.[42,43] The oxygen cost of "pressure work" is greater than "volume work," with the area-under-the-curve for LV pressure closely correlating with myocardial oxygen demand.[44] During the perioperative period, stress response is well reported, further exacerbating the balance of myocardial oxygen supply and demand, including patients with nonobstructive coronary artery stenoses.[45–47] As the disease advances, high ventricular

Table 3. Evidence Profile and Summary of Findings

Certainty Assessment							Control Event Rate	Estimate of Prognostic Association		
No. of Studies (No. of Patients)	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias and Considerations to Upgrade Certainty	Incidence Rate in Patients with No or Lower Grade PDD	Relative (95% CI)	Absolute	Reviewers' Certainty
Long-term cardiovascular death in open vascular surgeries (follow-up 12–368 weeks)										
1 (449)	Observational studies	Very serious*	No serious inconsistency	No serious indirectness	Serious†	Not detected and not applicable	2.5%	OR 3 (1.5–6)‡	46 more per 1,000 (from 12 more to 108 more)	Very low
Long-term cardiovascular death in endovascular surgeries (follow-up 12–368 weeks)										
1 (259)	Observational studies	Very serious*	No serious inconsistency	No serious indirectness	Serious†	Not detected and not applicable	3.9%	OR 1.7 (0.5–5.3)‡	26 more per 1,000 (from 19 fewer to 138 more)	Very low
Congestive heart failure/pulmonary edema (during hospitalization)										
3 (996)	Observational studies	Very serious§	No serious inconsistency	No serious indirectness	No serious imprecision	Not detected and not applicable	12%‖	OR 3.90 (2.23–6.83)	227 more per 1,000 (from 113 more to 362 more)	Low
30-day major adverse cardiovascular events										
4 (1,814)	Observational studies	Serious#	No serious inconsistency	No serious indirectness	No serious imprecision	Not detected and not applicable	5%‖	OR 2.03 (1.24–3.32)	47 more per 1,000 (from 11 more to 99 more)	Moderate
Myocardial infarction/ischemia (at 30 days or within period of hospitalization)										
3 (717)	Observational studies	Very serious**	No serious inconsistency	No serious indirectness	No serious imprecision	Not detected and not applicable	6%‖	OR 1.74 (1.14–2.67)	40 more per 1,000 (from 8 more to 86 more)	Low

Other outcomes: 30-day all-cause mortality, 30-day cardiovascular death, length of hospital stay, arrhythmia requiring treatment, and long-term all-cause mortality

Underpowered evidence with wide CIs crossing the null. A significant association between PDD and these outcomes could neither be confirmed nor be refuted—*i.e.*, inconclusive evidence

Levels of certainty about evidence

High: We are very confident that the true risk lies close to the estimated risk

Moderate: We are moderately confident in the estimated risk. The true risk is likely to be close to the estimated, but there is a possibility that it is substantially different

Low: Our confidence in the estimated risk is limited. The true risk may be substantially different from the estimated risk

Very low: We have very little confidence in the estimated risk. The true risk is likely to be substantially different from the estimated risk

*Did not adjust for important postsurgery long-term time-varying confounding (*e.g.*, life style, weight, management of comorbidities and utilization of health services, adherence to medications, *etc.*). †Small number of total events and wide CI implying that the estimate of association is fragile. ‡Partial adjustment for confounders. §Partially adjusted or unadjusted crude estimates (all high risk of bias studies). ‖Median incidence rate of the outcome as observed across the contributing studies in the control group with no or lower grade of left ventricular diastolic dysfunction. #Mix of low, moderate, and high risk of bias studies with 50% of the weight in the meta-analysis contributed by low to moderate risk of bias studies—overall moderate risk of bias evidence. **High risk of bias studies with unadjusted crude estimates.

OR= odds ratio; PDD = perioperative diastolic dysfunction.

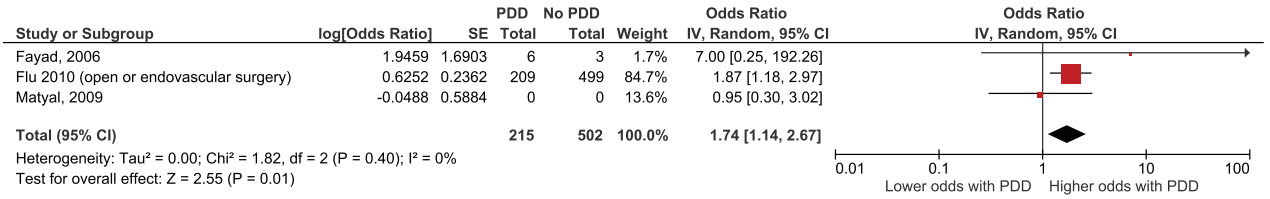

Fig. 7. Perioperative diastolic dysfunction (PDD) *versus* normal left ventricular diastolic function: myocardial infarction/ischemia during hospitalization after surgery or within 30 days. *df* = degrees of freedom; IV = inverse variance; SE = standard error.

filling pressure leads to high left atrial pressure and pulmonary venous hypertension that results in greater susceptibility to the development of flash pulmonary edema.[48,49] In the perioperative period, excessive fluid replacement and hemodynamic instability may trigger pulmonary edema at a lower threshold in patients with PDD.[50,51] Furthermore, a catecholamine surge in patients with diastolic dysfunction could potentially alter ventricular–atrial coupling, thereby increasing the risk of pulmonary edema/CHF and hemodynamic instability.[52,53] Additionally, occurrence of myocardial ischemia could be further contributing to the aggravation of pulmonary edema or CHF, with the two adverse events accounting for the higher incidence of MACE with PDD that we have observed.

Our claim of the incremental value of PDD as a predictor of adverse surgical outcomes over and above other risk factors such as hypertension, diabetes mellitus, and frailty that are already accounted for in existing cardiac risk prediction models might need to be taken with caution because of the limitations identified in the studies. However, we did appraise whether important confounding was adjusted in the design or analysis of individual studies. While most studies were at high risk of bias for inadequate control of confounding, cofounders were not identical across studies. Therefore, it is more likely that PDD is an independent risk factor in its own right rather than a surrogate for hypertension, diabetes, or frailty. A possible explanation for PDD as an independent risk predictor could be that the composite of age, history of hypertension, and diabetes may not adequately capture the real intensity and duration of exposure to the preexistent cardiovascular stresses that predispose to a higher risk of surgery.

We acknowledge a few limitations in the conduct of our systematic review. We accepted investigators' classification of PDD as long as at least one of the routine parameters was employed for classification of exposure. Guidelines recommend that diastolic dysfunction should be measured by at least two echo parameters to ensure reproducibility.[15] Only 2 of the 13 included studies defined PDD with a single echo parameter, yet neither were found to be outliers in the meta-analyses they were included in, allaying important concerns about systematic error in risk estimation.[31,34] We also accepted all investigator-defined parameter cutoff values unless deemed far from cutoff values employed in routine practice. Another limitation is that we did not consider the subjective assessment of PDD as a major limitation of study validity. However, blinded assessment of PDD and outcomes were important considerations in our critical appraisal of studies.

Despite the low level of certainty (as judged using the GRADE approach[23]) for the observed estimates of association, with moderate certainty, we can state that more patients will experience postoperative morbidity and mortality within 30 days of noncardiac surgery if they have PDD compared with those without diastolic dysfunction.

Conclusions and Future Research Recommendations

With moderate degree of certainty, we conclude that PDD is an independent risk factor for adverse cardiovascular outcomes after noncardiac surgery. We propose that future revisions of the ACC/AHA revised cardiac risk index or other risk prediction models in current use should consider PDD as an additional candidate risk predictor in model derivation studies. Such a study should ensure that assessment of PDD is rigorous and blinded with measures incorporated to minimize subjective interpretation of echo parameters. Even better would be to use the established echo parameters as continuous variables in the model as opposed to PDD grade categories. Subsequently, the comparative clinical effectiveness and cost-effectiveness of the earlier and revised versions of the model may be investigated if echo parameters make into the final revised model.

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Competing Interests

The authors declare no competing interests.

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Appendix 1. Database: Ovid MEDLINE(R) In-Process and Other Nonindexed Citations and Ovid MEDLINE(R) (1946 to Present) Search Strategy

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1 (ventricular function/ or ventricular function, left/) and Diastole/ (3861)
2 diastolic dysfunction.tw. (6289)
3 diastolic heart failure.tw. (1003)
4 (abnormal$ adj2 diastolic function).tw. (300)
5 or/1–4 (10155)
6 exp Perioperative Period/ (54703)
7 Intraoperative Complications/or Monitoring, Intraoperative/ (40672)
8 (perioperat$ or peri operat$ or periproced$ or peri proced$ or intraoperat$ or intra operat$ or intraproced$ or intra proced$ or postoperat$ or post operat$).tw. (511761)
9 or/6–8 (555803)
10 5 and 9 (358)
11 ((noncardiac or noncardiac) adj3 surg$).tw. (2831)
12 surgical procedures, operative/ or ambulatory surgical procedures/ or exp bariatric surgery/ or exp digestive system surgical procedures/ or drainage/ or exp endocrine surgical procedures/ or exp mastectomy/ or minimally invasive surgical procedures/ or exp obstetric surgical procedures/ or exp neurosurgical procedures/ or exp ophthalmologic surgical procedures/ or exp oral surgical procedures/ or exp orthopedic procedures/ or exp otorhinolaryngologic surgical procedures/ or exp reconstructive surgical procedures/ or thoracic surgical procedures/ or exp pulmonary surgical procedures/ or kidney transplantation/ or liver transplantation/ or lung transplantation/ or pancreas transplantation/ or ultrasonic surgical procedures/ or exp urogenital surgical procedures/ (1448455)
13 11 or 12 (1450242)
14 5 and 13 (177)
15 10 or 14 (494)
16 animals/ not humans/ (3931867)
17 15 not 16 (429)
18 limit 17 to english language (383)

Database: Embase Classic+Embase < 1947 to 2015 April 27 > Search Strategy:

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1 *diastolic dysfunction/ or left ventricular diastolic dysfunction/ (3028)
2 diastolic dysfunction.tw. (11420)
3 diastolic heart failure.tw. (1759)
4 (abnormal$ adj2 diastolic function).tw. (437)
5 or/1–4 (13232)
6 perioperative period/ (29879)
7 *peroperative complication/ (4632)
8 *patient monitoring/ (6637)
9 (perioperat$ or peri operat$ or periproced$ or peri proced$ or intraoperat$ or intra operat$ or intraproced$ or intra proced$ or postoperat$ or post operat$).tw. (715196)
10 or/6–9 (727884)
11 5 and 10 (362)
12 ((noncardiac or noncardiac) adj3 surg$).tw. (3844)
13 failed back surgery syndrome/ or foot surgery/ or pancreas surgery/ or brain surgery/ or endoscopic sinus surgery/ or tendon surgery/ or plastic surgery implant/ or ear surgery/ or shoulder surgery/ or thoracic aorta surgery/ or cornea surgery/ or knee ligament surgery/ or skull surgery/ or endoscopic surgery/ or decompression surgery/ or maxillofacial surgery/ or cancer surgery/ or face surgery/ or nerve surgery/ or general surgery/ or laparoendoscopic single site surgery/ or bladder surgery/ or kidney surgery/ or uterus surgery/ or exp hip surgery/ or male genital system surgery/ or skin surgery/ or pelvis surgery/ or knee surgery/ or spine surgery/ or exp orthopedic surgery/ or plastic surgery/ or retina surgery/ or urethra surgery/ or rectum surgery/ or aneurysm surgery/ or ambulatory surgery/ or anus surgery/ or exp eye surgery/ or esophagus surgery/ or thyroid surgery/ or ureter surgery/ or exp endocrine surgery/ or prostate surgery/ or spinal cord surgery/ or trachea surgery/ or colorectal surgery/ or refractive surgery/ or middle ear surgery/ or liver surgery/ or emergency surgery/ or geriatric surgery/ or urologic surgery/ or urinary tract surgery/ or spleen surgery/ or intestine surgery/ or exp ear nose throat surgery/ or abdominal surgery/ or laparoscopic surgery/ or elective surgery/ or colon surgery/ or “head and neck surgery”/ or throat surgery/ or biliary tract surgery/ or glaucoma surgery/ or aorta surgery/ or microvascular surgery/ or breast surgery/ or hand surgery/ or arthroscopic surgery/ or exp gastrointestinal surgery/ or gynecologic surgery/ or uterine tube surgery/ or joint surgery/ or bariatric surgery/ (1339755)
14 surgical patient/ (28762)
15 12 or 13 or 14 (1359747)
16 5 and 15 (208)
17 11 or 16 (502)
18 limit 17 to english language (471)
19 animals/ not humans/ (1244570)
20 18 not 19 (470)

Database: Cochrane Library

(*Continued*)

Appendix 1. (Continued)

IDSearchHits
#1 diastolic dysfunction:ti,ab,kw (Word variations have been searched)1309
#2 diastolic heart failure:ti,ab,kw1649
#3 (abnormal* near/2 diastolic function):ti,ab,kw36
#4 MeSH descriptor: [Ventricular Function] explode all trees2604
#5 MeSH descriptor: [Ventricular Function, Left] explode all trees1981
#6 #4 or #52604
#7 MeSH descriptor: [Diastole] explode all trees936
#8 #6 and #7208
#9 #1 or #2 or #3 or #82637
#10 MeSH descriptor: [Perioperative Period] explode all trees5846
#11 MeSH descriptor: [Monitoring, Intraoperative] explode all trees1319
#12 MeSH descriptor: [Intraoperative Complications] explode all trees3498
#13 (perioperat* or peri operat* or periproced* or peri proced* or intraoperat* or intra operat* or intraproced* or intra proced* or post-operat* or post operat*):ti,ab,kw (Word variations have been searched)74190
#14 #10 or #11 or #12 or #1375466
#15 #9 and #14127
#16 ((noncardiac or noncardiac) near/3 surg*):ti,ab,kw (Word variations have been searched)296
#17 MeSH descriptor: [Surgical Procedures, Operative] explode all trees101040
#18 MeSH descriptor: [Cardiac Surgical Procedures] explode all trees11845
#19 #17 not #1889195
#20 #16 or #1989365
#21 #9 and #20122
#22 #21 or #15221
Cochrane Database of Systematic Reviews: Issue 4 of 12, April 2015 = 18 results
Database of Abstracts of Reviews of Effect: Issue 1 of 4, January 2015 = 1 result
Cochrane Central Register of Controlled Trials: Issue 3 of 12, March 2015 = 202 results
Database: PubMed

((((((diastolic dysfunction[Title/Abstract]) OR diastolic heart failure[Title/Abstract]) OR abnormal* diastolic function[Title/Abstract])) AND ((((((noncardiac[Title/Abstract] AND surg*[Title/Abstract])) OR (noncardiac[Title/Abstract] AND surg*[Title/Abstract])) OR (surger*[Title/Abstract] OR surgical[Title/Abstract]))) OR ((((intraoperative*[Title/Abstract]) OR intra operative*[Title/Abstract]) OR perioperative*[Title/Abstract]) OR perioperative*[Title/Abstract]))))) AND ((((publisher[sb] or pubmednotmedline[sb])) OR pubstatusaheadofprint)) = 8 results

Appendix 2

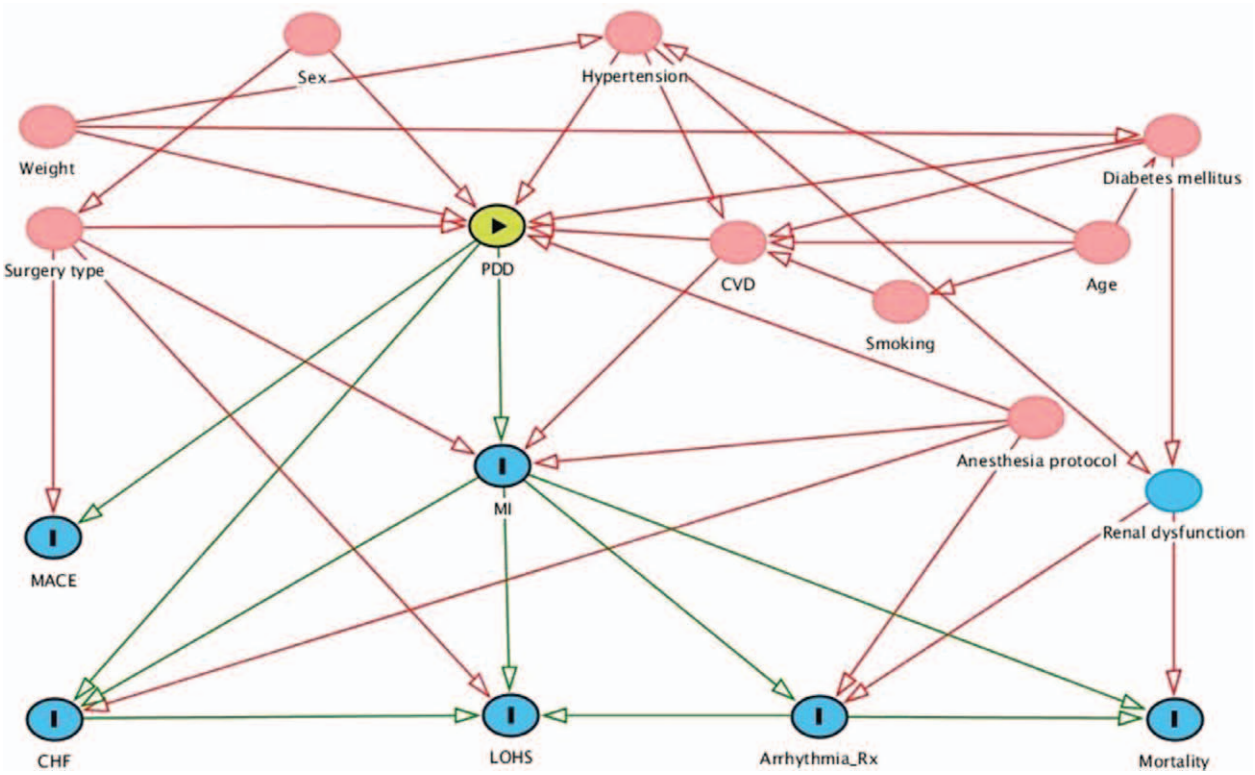

Fig. A2.1. Directed acyclic graph of causal relationships between covariates, exposure, and outcomes.

- exposure
- outcome
- ancestor of exposure
- ancestor of outcome
- ancestor of exposure *and* outcome
- causal path
- biasing path

Arrhythmia_Rx = arrhythmia requiring treatment; CHF = congestive heart failure; CVD = cardiovascular disease; LOHS = length of hospital stay; MACE = major adverse cardiovascular events; MI = myocardial infarction/ischemia; PDD = perioperative (left ventricular) diastolic dysfunction; postop = postoperative.

DAGitty minimal sufficient adjustment sets for adequate control of confounding bias:

- (Age or history of) cardiovascular disease, diabetes mellitus, hypertension, type of anesthesia, and type of surgery, or
- (Age or history of) cardiovascular disease, renal dysfunction, type of anesthesia, and type of surgery