Cardiac Troponins in Low-Risk Pulmonary Embolism Patients: A Systematic Review and Meta-Analysis

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BACKGROUND: Patients with low-risk pulmonary embolism (PE) should be considered as per current scoring systems for ambulatory treatment. However, there is uncertainty whether patients with low scores and positive troponins should require hospitalization.

METHODS: We searched MEDLINE, SCOPUS, and Cochrane Library databases from inception to December 2016 and collected longitudinal studies that evaluated the prognostic value of troponins in patients with low-risk PE. The primary outcome measure was 30-day all-cause mortality. We calculated odds ratio (OR), likelihood ratios (LRs), and 95% confidence intervals (CI) by using random-effects models.

RESULTS: The literature search identified 117 candidate articles, of which 16 met the criteria for review. Based on pulmonary embolism severity index (PESI) or sPESI score, 1.2% was the all-cause mortality rate across 2,662 participants identified as low-risk. A positive troponin status in patients with low-risk PE was associated with an increased risk of 30-day all-cause mortality (odds ratio [OR]: 4.79; 95% confidence interval [CI]: 1.11 to 20.68). The pooled likelihood ratios (LRs) for all-cause mortality were positive LR 2.04 [95% CI, 1.53 to 2.72] and negative LR 0~~.072~~ 0.72 [95% CI, 0.37 to 1.40].

CONCLUSION: The use of positive troponin status as a predictor of increased mortality in low-risk PE patients exhibited relatively poor performance given the crossed negative LR CI (1.0) and modest positive LR. Larger prospective trials must be conducted to elucidate if patients with low-risk PE and positive troponin status can avoid hospitalization. *Journal of Hospital Medicine* 2018;13:XXX-XXX. © 2018 Society of Hospital Medicine

Hospital stays for pulmonary embolism (PE) represent a significant cost burden to the US health care system.[1] The mean total hospitalization costs for treating a patient with PE ranges widely from $8,764 to $37,006, with an average reported length of stay between 4 and 5 days.[2,3] This cost range is attributed to many factors, including type of PE, therapy-induced bleeding risk requiring close monitoring, comorbidities, and social determinants of health. Given that patients with low-risk PE represent the majority of the cases, changes in approaches to care for this population can significantly impact the overall health care costs for PE. The European Society of Cardiology (ESC) guidelines incorporate well-validated risk scores, known as the pulmonary embolism severity index (PESI) and the simplified PESI score, and diagnostic test recommendations, including troponin test, echocardiography, and computed tomography, to evaluate patients with PE at varying risk for mortality.[4] In these guidelines, the risk stratification algorithm for patients with a low PESI score or a sPESI score of zero does not include checking for the presence of troponin. In reality, practicing hospitalists frequently find that patients receiving a work-up in the emergency department for suspected PE undergo troponin test. The ESC guidelines categorize patients with a low-risk score on PESI/sPESI, who subsequently have a positive troponin status, as intermediate low-risk and suggest consideration of hospitalization. The guidelines recommend patients with positive cardiac biomarkers to undergo assessment of right ventricular function through echocardiogram or computed tomography analysis. Moreover, the guidelines support early discharge or ambulatory treatment for low-risk patients who have a negative troponin status.[4]

The American College of Chest Physicians (ACCP) guidelines on venous thromboembolism (VTE) recommend that cardiac biomarkers should not be measured routinely in all patients with PE and that positive troponin status should discourage physicians from pursuing ambulatory treatment.[5] Therefore, ambiguity lies within both guidelines with regard to how hospitalists should interpret a positive troponin status in patients with low-risk, which in turn may lead to unnecessary hospitalizations and further imaging. This systematic review and meta-analysis aims to provide clarity, both about gaps in literature and about how practicing hospitalists should interpret troponin in patients with low-risk PE.

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TABLE 1. **Characteristics of the Studies**

Source	Year	#Patients	Age[a]	% Males	Study Design	Risk Score	Type of Troponin	Primary Endpoints
Ahn et al.[7]	2016	228	59 ± 11.3	51	R	PESI	cTnI	30 d, 3 mo, 6 mo A-C mortality
Ozsu et al.[8]	2015	206	71 (58–80)	40	P	sPESI	cTnI, cTnT	90 d A-C mortality
Hakemi et al.[9]	2015	298	56 (±13)	51	R	PESI	hs-cTnI	5 d median eventsb
Lauque et al.[10]	2014	132	69 (±21)	51	P	PESI	cTnI-ultra	30 d A-C mortality & eventsc
Vuilleumier et al.[11]	2014	230	75 (69–82)	59	P	PESI	hs-cTnT	30 d eventsd
Jimenez et al.[12]	2014	848	72 (59–80)	49	P	sPESI	cTnI	30 d A-C mortality & eventse
Ozsu et al.[13]	2013	121	70 (55–76)	43	P	sPESI	cTnT, hsTnT	30 d A-C mortality
Sanchez et al.[14]	2013	529	67 (52–77)	47	P	PESI	cTnI	30 d A-C mortality & eventsf
Barra et al.[15]	2012	142	70 ± 15	40	R	sPESI	cTnI	30 d A-C mortality
Lankeit et al.[16]	2011	526	71 (55–79)	51	P	sPESI	hs-cTnT	30 d A-C mortality & eventsg
Sanchez et al.[17]	2011	1291	74 (61–80)	45	R	sPESI	cTnI	30 d A-C mortality
Spirk et al.[18]	2011	369	67 (±21)	53	P	sPESI	cTn I or T, hs-TnT	30 d A-C mortality & recurrent PE
Vanni et al.[19]	2011	463h	>65 (73)	43.7	P	PESI	cTnI	In-hospital A-C & PE-related deaths
Jimenez et al.[20]	2011	591	74 (65–82)	43	P	PESI	cTnI	30 day PE-related mortality
Singanayagam et al.[21]	2010	411	>65 (55)	43.1	R	PESI	cTnI	30 day A-C mortality
Moores et al.[22]	2009	567	>65 (74)	43	P	PESI	cTnI	30 day A-C mortality

Abbreviations: A-C, all-cause; P, prospective; R = Retrospective.
[a]Age is given as mean (±SD) or median (IQ) or >65 years (%)
[b]In-hospital death/CPR/ thrombolytic therapy
[c]cardiac arrest/CPR/ mechanical ventilation/ need for catecholamine support/recurrence of acute PE
[d]PE related death, recurrence of VTE, and major bleeding
[e]hemodynamic collapse, and/or recurrent PE
[f]secondary cardiogenic shock, or confirmed symptomatic recurrent VTE
[g]catecholamine support/endotracheal intubation/CPR
[h]Total was 510, but 463 pts were stratified using PESI
Secondary events were mostly not available except for the following studies: Ozsu 2015 = nonfatal symptomatic recurrent PE or nonfatal major bleeding; Lankeit= Recurrent PE/Major bleeding; Sanchez 2011=PE Related Mortality; Vanni= nonfatal PE recurrence/delayed hemodynamic instability/nonfatal major bleeding

METHODS

Data Sources and Searches

This systematic review and meta-analysis was performed in accordance with the established methods and Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. We searched MEDLINE, SCOPUS, and Cochrane Controlled Trial Registry databases for studies published from inception to December 2016 by using the following key words: pulmonary embolism AND PESI OR "pulmonary embolism severity index." Only articles written in English language were included. The full articles of potentially eligible studies were reviewed, and articles published only in abstract form were excluded.

Study Selection

Two investigators independently assessed the abstract of each article, and the full article was assessed if it fulfilled the following criteria: 1) the publication must be original; 2) inclusion of objectively diagnosed, hemodynamically stable patients (normotensive patients) with acute PE in the inpatient or outpatient setting; 3) inclusion of patients ≥ 19 years old; 4) use of the PESI or sPESI model to stratify patients into a low-risk group irrespective of any evidence of right ventricular dysfunction; and 5) testing of cardiac troponin levels (TnI-troponin I, TnT-troponin T, or hs-TnI/TnT-high sensitivity troponin I/T) in patients. Study design, sample size, duration of follow-up, type of troponin used, definition of hemodynamic stability, and specific type of outcome measured (endpoint) did not affect the study eligibility.

Data Extraction and Risk of Bias Assessment

For each eligible article, we abstracted information and created 2 tables. Table 1 shows the study characteristics, and Supplementary Table 1 presents the outcomes of each individual study and the pooled outcomes. In cases where information regarding the specific number of outcomes from the paper is missing, we emailed the primary author. Two investigators independently evaluated studies that were included in the meta-analysis using the methodological risk of bias in accordance

TABLE 2. **Summary Measures of the Association between Troponin Classification and Overall 30-day All-cause Mortality and Stratified by Study**

Source	Low-risk PE Patients	Tn+	Tn-	PPV	NPV	PLR (95% CI)		NLR (95% CI) OR (95% CI)		Odds Ratio p		
Ozsu et al.[8]	57	5	52									
90-day mortality	4	3	1	0.60	0.98	19.88	(4.56–86.66)	0.26	(0.05–1.42)	76.50	(5.31–1102.4)	0.0014
Hakemi et al.[9]	173	84	89									
In-hospital mortality	4	4	0	0.05	1.00	1.90	(1.36–2.65)	0.19	(0.01–2.64)	10.01	(0.53–188.75)	0.1243
Lauque et al.[10]	84	17	67									
30-day mortality	1	1	0	0.06	1.00	3.82	(1.54–9.48)	0.31	(0.03–3.44)	12.27	(0.48–315.11)	0.1300
Ozsu et al.[13]	45	14	31									
30-day mortality	0	0	0	0.00	1.00	1.59	(0.21-11.79)	0.73	(0.10-5.23)	2.17	(0.04–114.99)	0.7016
Sanchez et al.[14]	329	44	278									
30-day mortality	2	NS	NS	NS	NS	NS	—	NS	—	NS	—	—
Lankeit et al.[16]	198	71	127									
30-day mortality	1	1	0	0.01	1.00	2.11	(0.93–4.79)	0.39	(0.04-4.29)	5.43	(0.22–134.95)	0.3024
Moores et al.[22]	191	42	149									
30-day mortality	1	0	1	0.00	0.99	1.12	(0.10–12.57)	0.97	(0.43-2.16)	1.16	(0.05–29.11)	0.9260
All studies pooled[a]	691	228	~~691~~ 463									
30-day mortality[b]	7	6	1	0.03	1.00	2.04	(1.53–2.72)	0.72	(0.37–1.40)	4.79	(1.11–20.68)	0.0357
Sensitivity Analysis[c]						3.40	(1.81–6.37)	0.59	(0.33–1.08)	11.01	(3.38–35.92)	<0.0001

Abbreviations: NLR, negative likelihood ratio; NS, data not supplied; NPV, negative predictive value, PLR, positive likelihood ratio, PPV, positive predictive value.
[a]Total number of low risk PE patients, Tn+, Tn-
[b]Pooled estimates of PPV, NPV, PLR, NLR, and OR for 30-day all-cause mortality do not include data from the Ozsu[8] and Sanchez[14] studies.
[c]Includes the Ozsu 2015 study and assumes the 2 PE patients with mortalities in the Sanchez 2013 were from troponin positive

with the *Cochrane Handbook for Systematic Reviews of Interventions*. Each study was judged as being low, moderate, or high risk of bias (Supplementary Table 2). Disagreements were resolved with discussion between the 2 primary reviewers and obtaining a third opinion.

Statistical Analysis

Data were summarized by using 30-day all-cause mortality only because it is the most consistent endpoint reported by all of the included studies. For each study, 30-day all-cause mortality was analyzed across the 2 troponin groups, and the results were summarized in terms of positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR), and odds ratio (OR). To quantify the uncertainty in the LRs and ORs, we calculated 95% confidence intervals (CI).

Overall measures of PPV, NPV, PLR, and NLR were calculated on the pooled collection of data from the studies. LRs are one of the best measures of diagnostic accuracy; therefore, we defined the degree of probability of disease based on simple estimations that were reported by McGee.[6] These estimations are independent of pretest probability and include the following: PLR 5.0 increases the probability of the outcome by about 30%, whereas NLR 0.20 decreases the probability of the outcome by 30%. To identify reasonable performance, we defined a PLR > 5 as an increase in moderate to high probability and a NLR < 0.20 as a decrease in moderate to high probability.[6]

The overall association between 30-day all-cause mortality and troponin classification among patients with low-risk PE was assessed using a mixed effects logistic regression model. The model included a random intercept to account for the correlation among the measurements for patients within a study. The exponentiated regression coefficient for troponin classification is the OR for 30-day all-cause mortality, comparing troponin-positive patients to troponin-negative patients. OR is reported with a 95% confidence interval and a *P* value. A continuity correction (correction = 0.5) was applied to zero cells. Heterogeneity was measured using Cochran Q statistic and Higgins I^2 statistic.

RESULTS

Search Results

Figure 1 represents the PRISMA flow diagram for literature search and selection process to identify eligible studies for inclusion.

Study Characteristics

The abstracts of 117 articles were initially identified using the search strategy described above. Of these, 18 articles were deemed appropriate for review based on the criteria outlined

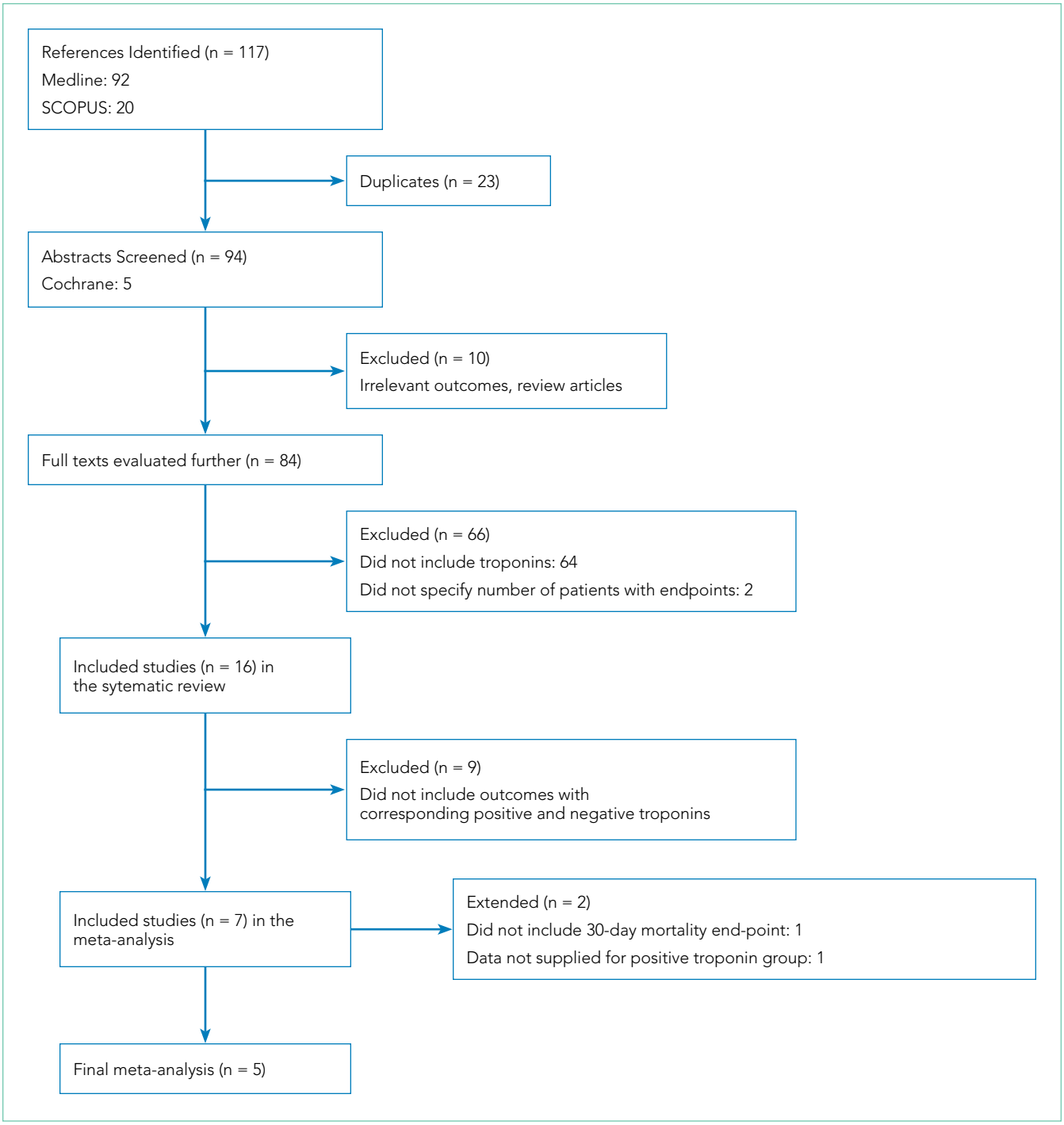

FIG 1. Flow Diagram for Study Selection

in "Study Selection." The full-text articles of the selected studies were obtained. Upon further evaluation, we identified 16 articles (Figure 1) eligible for the systematic review. Two studies were excluded because they did not provide the number of study participants that met the primary endpoints. The included studies were published from 2009–2016 (Table 1). For patients with low-risk PE, the number of patients with RV dysfunction was either difficult to determine or not reported in all the studies.

Regarding study design, 11 studies were described as prospective cohorts and the remaining 5 studies were identified as retrospective (Table 1). Seven studies stratified participants' risk of mortality by using sPESI, and 8 studies employed the PESI score. A total of 6,952 participants diagnosed with pulmonary embolism were obtained, and 2,662 (38%) were recognized as being low-risk based on either the PESI or sPESI. The sample sizes of the individual studies ranged from 121 to 1,291. The studies used either hs-cTnT, hs-cTnI, cTnT, cTnI, or

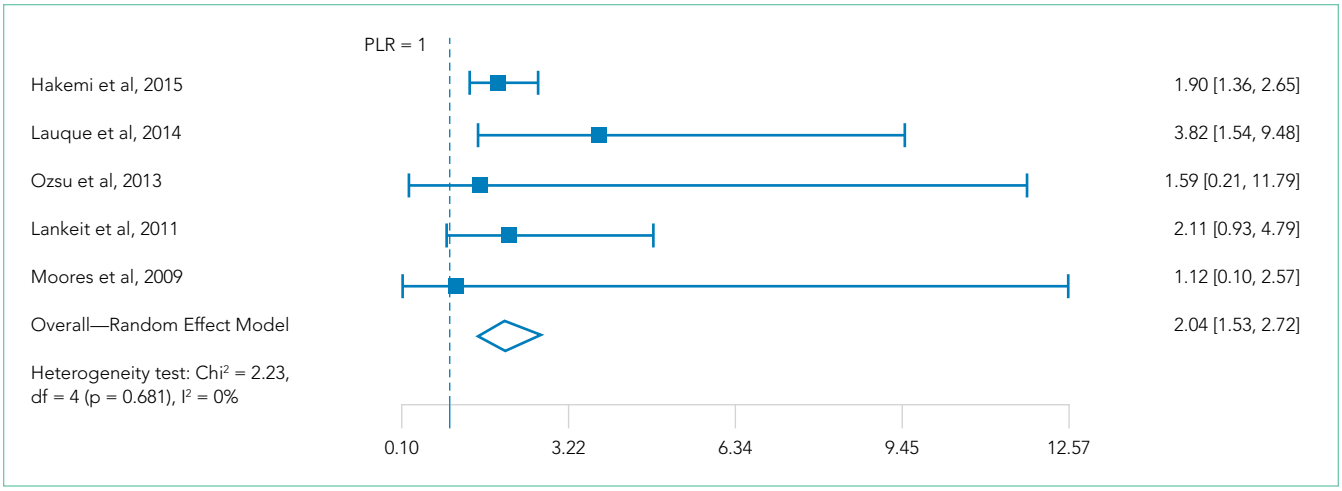

FIG 2. Positive Likelihood Ratio Forest Plot

a combination of hs-cTnT and cTnI or cTnT for troponin assay. Most studies used a pre-defined cut-off value to determine positive or negative troponin status.

Thirteen studies reported 30-day event rate as one of the primary endpoints. The 3 other studies included 90-day all-cause mortality, and 2 of them included in-hospital events. Secondary event rates were only reported in 4 studies and consisted of nonfatal PE, nonfatal major bleeding, and PE-related mortality.

Our systematic review revealed that 5 of the 16 studies used either hemodynamic decompensation, CPR, mechanical ventilation, or a combination of any of these parameters as part of their primary or secondary endpoint. However, none of the studies specified the number of patients that reached any of these endpoints. Furthermore, 10 of the 16 studies did not specify 30-day PE-related mortality outcomes. The most common endpoint was 30-day all-cause mortality, and only 7 studies reported outcomes with positive or negative troponin status.

Outcome Data of All Studies

A total of 2,662 participants were categorized as being low risk based on the PESI or sPESI risk score. The pooled rate of PE-related mortality (specified and inferred) was 5 (0.46%) from 6 studies (1,093 patients), in which only 2 studies specified PE-related mortality as the primary endpoint [Vanni (2011) and Jimenez (2011)]. The pooled rate of 30-day all-cause mortality was 24 (1.3%) from 12 studies (1,882 patients). In 14 studies (2,163 patients), the rates of recurrence of PE and major bleeding were 3 (0.14%) and 6 (0.28%), respectively.

Outcomes of Studies with Corresponding Troponin+ and Troponin –

Seven studies used positive or negative troponin status as endpoint to assess low-risk participants (Table 2). However, only 5 studies were included in the final meta-analysis because some data were missing in the Sanchez[14] study and the Oszu[8] study's mortality end-point was more than 30 days. The risk of bias within the studies was evaluated, and for most studies, the quality was of moderate degree (Supplementary Table 1). Table 2 shows the results for the overall pooled data stratified by study. In the pooled data, ~~691~~ (~~75%~~) patients tested negative for troponin and 228 (~~23%~~) tested positive. The overall mortality (from sensitivity analysis) including in-hospital, 30-day, and 90-day mortalities was 1.2%. The NPVs for all individual studies and the overall NPV are 1 or approximately 1. The overall PPVs and by study were low, ranging from 0 to 0.60. The PLRs and NLRs were not estimated for an outcome within an individual study if none of the patients experienced the outcome. When outcomes were only observed among troponin-negative patients, such as in the study of Moore (2009) who used 30-day all-cause mortality, the PLR had a value of zero. When outcomes were only observed among troponin-positive patients, as for 30-day all-cause mortality in the Hakemi[9](2015), Lauque[10](2014), and Lankeit[16](2011) studies, the NLR had a value of zero. For zero cells, a continuity correction of 0.5 was applied. The pooled likelihood ratios (LRs) for all-cause mortality were positive LR 2.04 [95% CI, 1.53 to 2.72] and negative LR ~~0.072~~ [95% CI, 0.37 to 1.40]. The OR for all-cause mortality was 4.79 [95% CI 1.11 to 20.68, *P* = .0357].

A forest plot was created to visualize the PLR from each study included in the main analysis (Figure 2).

A sensitivity analysis among troponin-positive patients was conducted using 90-day all-cause mortality outcome from the study of Ozsu[8] (2015) and the 2 all-cause mortality outcomes from the study of Sanchez[14] (2013). The pooled estimates from the 30-day all-cause mortality differed slightly from those previously reported. The PLR increased to 3.40 [95% CI 1.81 to 6.37], and the NLR decreased to 0.59 [95% CI 0.33 to 1.08].

DISCUSSION

In this meta-analysis of 5 studies, which included 691 patients with low-risk PESI or sPESI scores, those tested positive for troponin had nearly a fivefold increased risk of 30-day all-cause mortality compared with patients tested negative. However, the clinical significance of this association is unclear given that the confidence interval (CI) is quite wide and mortality could

463 (67%)
(33%)
0.72

be associated with PE versus other causes. Similar results were reported by other meta-analyses that consisted of patients with normotensive PE.[23,24,25] To our knowledge, the present meta-analysis is the first to report outcomes in patients with low-risk PE stratified by the presence of cardiac troponin.

A published paper on simplifying the clinical interpretation of LRs state that a positive LR of greater than 5 and a negative LR of less than 0.20 provide dependable evidence regarding reasonable prognostic performance.[6] In our analysis, the positive LR was less than 5 and the negative LR's CI included one. These results suggest a small statistical probability that a patient with a low PESI/sPESI score and a positive troponin status would benefit from inpatient monitoring; simultaneously, a negative troponin does not necessarily translate to safe outpatient therapy, based on our statistical analysis. Previous studies also reported nonextreme positive LRs.[23,24] We therefore conclude that low-risk PE patients with positive troponins may be eligible for safe ambulatory treatment or early discharge. However, the number of outcomes of interest (mortality) occurred in only 6 patients among the 228 patients who had positive troponin status. The majority of deaths were reported by Hakemi et al.[9] in their retrospective cohort study; as such, drawing conclusions is difficult. Furthermore, the low 30-day all-cause mortality rate of 2.6% in the positive troponin group may have been affected by close monitoring of the patients, who commonly received hemodynamic and oxygen support. Based on these factors, our conclusion is relatively weak, and we cannot recommend a change in practice compared to existing guidelines. In general, additional prospective research is needed to determine whether patients with low-risk PE tested positive for troponin can receive care safely outside the hospital or, rather, require hospitalization similar to patients with high-risk PE.

We identified a number of other limitations in our analysis. First, aside from the relatively small number of pertinent studies in the literature, most of the studies are of low-moderate quality. Second, the troponin classification in various studies was not conducted using the same assay, and the cut-off value determining positive versus negative results in each case may have differed. These differences may have created some ambiguity or misclassification when the data were pooled together. Third, although the mixed effects logistic regression model controls for some of variations among patients enrolled in different studies, significant differences exist in terms of patient characteristics or the protocol for follow-up care. This aspect was unaccounted for in this analysis. Lastly, pooled outcome events could not be retrieved from all of the included studies, which would have resulted in a misrepresentation of the true outcomes.

The ESC guidelines suggest avoiding cardiac biomarker testing in patients with low-risk PE because this practice does not have therapeutic implications. Moreover, ESC and ACCP guidelines both state that a positive cardiac biomarker should discourage treatment out of the hospital. The ACCP guidelines further encourage testing of cardiac biomarkers and/or evaluating right ventricular function via echocardiography when uncertainty exists regarding whether patients may require close in-hospital monitoring or not. Although no resounding evidence suggests that troponins have therapeutic implications in patients with low-risk PE, the current guidelines and our meta-analysis cannot offer an overwhelmingly convincing recommendation about whether or not patients with low-risk PE and positive cardiac biomarkers are best treated in the ambulatory or inpatient setting. Such patients may benefit from monitoring in an observation unit (eg, less than 24 or 48 hours), rather than requiring a full admission to the hospital. Nevertheless, our analysis shows that making this determination will require prospective studies that will utilize cardiac troponin status in predicting PE-related events, such as arrhythmia, acute respiratory failure, and hemodynamic decompensation, rather than all-cause mortality.

Until further studies, hospitalists should integrate the use of cardiac troponin and other clinical data, including those available from patient history, physical exam, and other laboratory testing, in determining whether or not to admit, observe, or discharge patients with low-risk PE. As the current guidelines recommend, we support consideration of right ventricular function assessment, via echocardiogram or computed tomography, in patients with positive cardiac troponins even when their PESI/sPESI score is low.

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