Acute Mortality in Critically Ill Patients Undergoing Echocardiography With or Without an Ultrasound Contrast Agent

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OBJECTIVES The objective of this observational study was to compare 48-h all-cause mortality (as well as hospital stay mortality) among critically ill patients who underwent echocardiography either with or without an ultrasound contrast agent (UCA).

BACKGROUND The safety of perfluorcarbon-based UCAs has been questioned by the U.S. Food and Drug Administration (particularly when administered to critically ill patients) following rare reports of deaths or life-threatening adverse reactions that occurred in close temporal relationship to UCA administration.

METHODS This was a retrospective observational outcome study conducted in critically ill patients to compare all-cause 48-h and hospital stay mortality subsequent to echocardiography procedures performed either with or without a UCA. The study utilized discharge data from a database maintained by Premier, Inc. (Charlotte, North Carolina). Premier’s database is the largest U.S. hospital-based, service-level comparative database for quality and outcomes research, and provides detailed resource utilization data along with patients’ primary and secondary diagnoses and procedure billing codes. A propensity score–matching algorithm between UCA-enhanced echocardiography patients and non–contrast-enhanced echocardiography patients was utilized to reduce the potential for imbalance in covariates of selected patients in the comparison of mortality between groups.

RESULTS Patients undergoing echocardiography with a UCA had lower mortality at 48 h compared with patients undergoing non–contrast-enhanced echocardiography (1.70% vs. 2.50%), with an odds ratio = 0.66 (95% confidence interval [CI]: 0.54 to 0.80). Patients undergoing echocardiography with a UCA had lower hospital stay mortality compared with patients undergoing noncontrast echocardiography (14.85% vs. 15.66%), with an odds ratio = 0.89 (95% CI: 0.84 to 0.96).

CONCLUSIONS In critically ill, propensity-matched hospitalized patients undergoing echocardiography, use of a UCA is associated with a 28% lower mortality at 48 h in comparison with patients undergoing non–contrast-enhanced echocardiography. These results are reassuring, given previous reports suggesting an association between UCAs and increased mortality in critically ill patients. (J Am Coll Cardiol Img 2014;7:40–8) © 2014 by the American College of Cardiology Foundation
Transthoracic echocardiography (TTE) is an inexpensive, portable, safe, and reliable imaging tool used to evaluate cardiac structure and function. In critically ill patients, echocardiographic imaging is an essential component of care and provides data that alter immediate patient management. In the intensive care unit (ICU), echocardiograms are limited in quality in over 30% of studies because of obesity, severe pulmonary disease, and mechanical ventilation (1). However, most nondiagnostic echocardiography studies can be salvaged with ultrasound contrast agents (UCA) (1,2). As a result, judicious UCA use is now recommended by the American Society of Echocardiography and the combined specialty Appropriate Use Criteria for Echocardiography (3,4). The objective of this observational study was to compare 48-h all-cause mortality (as well as hospital stay mortality) among critically ill patients who underwent echocardiography either with or without a UCA.

**METHODS**

This was a retrospective observational outcome study conducted in critically ill patients to compare all-cause 48-h and hospital stay mortality subsequent to echocardiography procedures performed either with or without a UCA. The study used a propensity score–matching algorithm between UCA-enhanced echocardiography patients and nonenhanced echocardiography patients to reduce the potential for imbalance in covariates of selected patients in the comparison of mortality between groups. The study tested the primary hypothesis that there is no difference in 48-h all-cause mortality between the non–contrast-enhanced and UCA-enhanced groups using an odds ratio obtained from a mortality analysis of the propensity-matched study population.

The study utilized discharge data from a database maintained by Premier, Inc. (Charlotte, North Carolina). Premier’s database is the largest U.S. hospital-based, service-level comparative database for quality and outcomes research, and provides detailed resource utilization data along with patients’ primary and secondary diagnoses and procedure billing codes. Patient diagnoses and procedures in the Premier database are coded using the International Classification of Diseases–9th Revision–Clinical Modification (ICD-9-CM) classification system. The Premier database contains over 2.5 billion daily service records of patients from 750 geographically diverse hospitals, and about 45 million records are added each month. This is approximately 1 in every 4 discharges (26%) from U.S. hospitals. The demographics and baseline patient and hospital characteristics collected from the Premier database for use in this study are listed in Table 1.

A previous large retrospective study of 4,300,966 consecutive patients, using the Premier database,
demonstrated significantly lower acute mortality (odds ratio: 0.76; 95% confidence interval [CI]: 0.70 to 0.82) in all hospitalized patients undergoing UCA-enhanced echocardiography compared with all patients undergoing unenhanced echocardiography (5). On the basis of the results of this study, we assumed an unadjusted odds ratio point estimate of 0.80 for our primary hypothesis.

Forty-eight-hour all-cause mortality was defined as a discharge code of expired on the same day or in the 24-h period following echocardiography. Hospital stay mortality was defined as a discharge code of expired on the same day, or on the day following echocardiography where the time between echocardiography and the discharge code (measured in service days) was >2.

**Matched sample.** Contrast-enhanced TTE (cTTE) and non–contrast-enhanced TTE (nTTE) patients were matched using propensity score–matching techniques. The propensity score for subject \(i\) \((i = 1,...,N)\) is the conditional probability of being assigned to the UCA group \(Z_i = 1\) versus the noncontrast echocardiography group \(Z_i = 0\), given a vector of \(x_i\) of observed covariates. The propensity score can be thought of as a balancing score, that is, as a function \(b(X)\) of the observed covariates such that a conditional distribution of \(X\) given \(b(X)\) is the same for the UCA group \((Z = 1)\) and noncontrast echocardiography group \((Z = 0)\) of subjects.

The propensity score was calculated using logistic regression and included the following patient and provider characteristics:

- Age;
- Race;
- Admission type;
- Admission source;
- Sex;
- 3M All Patient Refined Diagnosis Related Groups (APR-DRG) (3M Health Information Systems, Salt Lake City, Utah) severity of illness assignment;
- 3M APR-DRG risk of mortality assignment;
- Discharge status;
- Attending physician specialty;
- Select comorbidities (defined as congestive heart failure, ventricular arrhythmias, hypertension, renal failure, venous catheterization for renal dialysis, hemodialysis, peritoneal dialysis, diabetes mellitus, chronic obstructive lung disorder, pneumonia, stroke, sepsis, septic shock, anaphylactic shock, gastrointestinal hemorrhage, transfusion procedure, myocardial infarction, acute coronary syndrome, pulmonary hypertension, intra-aortic balloon pump, cardiogenic shock, continuous positive airway pressure use, or mechanical ventilation);
• Hospital size (defined as the number of licensed, acute care beds);
• Hospital teaching status;
• Hospital geographic region (defined as Northeast, South, Midwest, or West); and
• Hospital population served (urban or rural).

These clinical and demographic covariates were selected because of their potential association with the outcome, or potential confounding effects as identified in the research reports (7).

For matching, the goal was to balance power (sample size) and precision (matching digit), with the equal distribution of patient and provider covariates (bias reduction) (8). Thus, patient and provider covariates were compared at the 3rd, 5th, and 7th propensity-matching digits to determine the optimal cutoff. Because the distribution of covariates remained relatively similar, and the absolute difference in propensity scores diverged at the second propensity digit, a 3-digit match was selected. The final analytical dataset contained 16,217 cTTE and 16,217 nTTE patients. Figure 1 illustrates the flow of the matching sequence.

Statistical analysis. All database management and statistical analyses were performed in SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina). Standard descriptive summaries included the mean, standard deviation, median, and range for continuous variables, and the frequency and percent of sample for categorical variables. All statistical tests of comparisons were 2-sided based on a 5% level of significance. Student t tests were used for comparisons of continuous variables, and chi-square tests for comparisons of categorical variables.

To evaluate the primary and secondary outcomes, a multivariate logistic regression model was used, and the model fitness was evaluated using likelihood-ratio, Hosmer-Lemeshow goodness of fit, and Concordance c statistics. The final model contained these covariates: treatment (cTTE or nTTE), age (grouped: 18 to 44, 45 to 64, 65 to 74, 75 to 79, or ≥80 years), sex, hemodialysis procedure, sepsis, transfusion procedure, continuous positive airway pressure use, and urban versus rural population served by the hospital. Although all of these covariates were used in the creation of the propensity-matched dataset, the aforementioned covariates remained significantly different between the 2 matched groups and were included to further control for potential confounding effects because of the imbalance between the cTTE and nTTE groups.

A sensitivity analysis was conducted to evaluate the potential influence of the matching precision on the primary outcome. Three-, 5-, and 7-digit–matched datasets were constructed representing 16,217 (3 digit), 15,775 (5 digit), and 10,343 (7 digit) patients in each matched group. The multivariate logistic regression model described in the previous text was run on each dataset and the findings compared using a Friedman test. Several subgroup analyses were also conducted using the same statistical methodology as that of the primary outcome.

**RESULTS**

The full dataset of patients that met the selection criteria for this study consisted of 1,006,381...
patients. Of those, 990,159 were included in the nTTE group, and 16,222 were included in the cTTE group. Patient demographics for the full dataset are summarized in Table 2, and results of the propensity score matching are shown in Table 3. The primary analysis was performed at 3 digits because this met the criteria recommended by Austin (9) and captured 99.97% of UCA echocardiography patients. Significant differences in baseline demographic variables and extent, and severity of comorbid conditions that had existed between cTTE and nTTE patients in the full dataset were resolved by including these covariates in the multivariate model (Tables 4 and 5).

The primary endpoint of 48-h mortality was also analyzed using 3-, 5-, and 7-digit propensity-matched datasets for added sensitivity. Although the sample sizes varied between the 3-, 5-, and 7-digit propensity-matched patient samples, 48-h mortality and the 95% Wald CIs were roughly equivalent (Friedman’s chi-square test = 0.72). At 3-digit–matched data, cTTE mortality was lower than nTTE mortality (2.18% vs. 2.97%), with an odds ratio of 0.72 (95% CI: 0.63 to 0.83). At 5-digit–matched data, cTTE mortality was lower than nTTE mortality (2.12% vs. 2.92%), with an odds ratio = 0.71 (95% CI: 0.62 to 0.82). For 7-digit–matched data, cTTE mortality was lower than nTTE mortality (1.70% vs. 2.50%), with an odds ratio of 0.66 (95% CI: 0.54 to 0.80) (Figs. 2 and 3).

When mortality throughout the entire hospital stay was assessed, the matched dataset at 3 digits showed that cTTE patients had a mortality rate of 14.85%, and nTTE patients had a mortality rate of 15.66% (Fig. 4). This finding was largely consistent across a wide variety of major comorbid conditions and important demographic subgroups such as age and sex (Table 6). Of note, there is striking concordance of the results across subgroups, many of which show statistically significantly lower odds ratios for mortality after cTTE than after nTTE. Also, there are no subgroups in which significantly greater odds ratios are seen after cTTE.

**DISCUSSION**

In October 2007, the U.S. Food and Drug Administration (FDA) mandated significant product labeling changes for UCAs following reports of post-contrast adverse reactions, including rare fatalities, which appeared to be temporally related, though not clearly causally attributable to UCA administration (10). The present study was
requested by the FDA to better define the risk–benefit relationship associated with cTTE in critically ill patients.

Three previously published studies evaluated acute mortality in hospitalized patients undergoing echocardiography with or without a UCA. The first study was a retrospective study performed at Saint Luke’s Mid America Heart Institute in Kansas City. In this report, Kusnetzky et al. (11) compared acute mortality in all hospitalized patients undergoing echocardiography with a UCA (n = 6,196) to those patients who did not receive a UCA (n = 12,475). Patients who received a UCA exhibited higher clinical acuity and more comorbidity than patients undergoing unenhanced echocardiography. Despite the fact that more critically ill patients received a UCA, there was no increase in 24-h mortality in patients receiving the UCA (mortality rate = 0.42% in the UCA arm and 0.37% in the cTTE arm, p = 0.60). Of note, this study did not employ propensity matching.

In a second retrospective study that utilized the Premier Hospital database (which included all hospitalized patients, not just the critically ill), Main et al. (5) evaluated 1-day mortality in 4,300,966 hospitalized patients who underwent echocardiography with a UCA (n = 58,254) or who underwent unenhanced echocardiography (n = 4,242,712). Unadjusted mortality was similar for both groups (UCA mortality at 1 day was 1.06% vs. 1.08% for unenhanced studies [p = 0.613]). A multivariate regression analysis adjusting for key baseline covariates revealed that patients who received a UCA were 24% less likely to die within 1 day as compared with patients who underwent unenhanced echocardiography (odds ratio = 0.76, 95% CI: 0.70 to 0.82).

A third study, similar in design to ours, but smaller in size, was also previously published (12). The results indicated no significant difference in mortality in the cTTE group compared with the nTTE group (odds ratio = 1.18; 95% CI: 0.82 to 1.71; p = 0.37).

In the current study, we have shown an association with lower mortality in critically ill patients undergoing echocardiography with a UCA, in comparison with propensity-matched patients undergoing echocardiography without a UCA. A sensitivity analysis comparing the mortality findings also confirmed the association with lower mortality in all matched patient populations (3 digit, 5 digit, and 7 digit). The inclusion of a wide range of clinical and demographic characteristics in the propensity score generation controlled for potential bias because of differences in patient and provider characteristics. The etiology of the association between UCA use and lower mortality is not clear. Possible explanations include better patient management decisions resulting from more timely and accurate diagnosis following contrast-enhanced echocardiography, the avoidance of downstream invasive tests, or both. Kurt et al. (1) recently showed in a single-center prospective study of 632 consecutive UCA-enhanced echocardiograms that contrast echocardiography was associated with improved image quality, and reduced both the number of uninterpretable echocardiography studies and the number of unevaluable left ventricular segments. This resulted in significant improvements in the evaluation of left ventricular function, better detection or exclusion of left ventricular thrombus.
and frequent changes in patient management as a result of better diagnostic information.

The present study builds on these previous reports in that: 1) the design of the current analysis was prospectively approved by the FDA; 2) the study included only critically ill, hospitalized patients; and 3) rigorous propensity score matching was utilized to reduce baseline differences between the contrast and noncontrast echocardiography groups.

Study limitations. The limitations include lack of information on the exact time or cause of death. However, biases were minimized by selecting all-cause mortality as the primary endpoint for outcomes assessments. The absence of temporal information on the timing of death was similarly mitigated using the all-cause mortality endpoint and evaluating mortality at 48 h and throughout the hospital stay.

Similarly, the use of propensity score matching addressed the potential for differences in patient clinical and demographic factors. Despite the
application of propensity matching of comparator groups of patients, this nonrandomized observational study could still be subject to hidden biases related to patient selection due to unadjusted differences in the patient populations in the UCA-enhanced and non–contrast-enhanced echocardiography groups. For example, administrative databases possess limited granularity. Patients with widely divergent illness acuity could be classified with the same ICD-9 code. It is likely, but not certain, that these differences are distributed relatively evenly between the UCA and noncontrast echocardiography groups. Nevertheless, the large size of this study, concordance of results across matches of varying precision, persistence of mortality reduction throughout hospital stay, and concordance of results across multiple comorbid conditions provide substantial evidence that UCA-enhanced echocardiography is associated with improved outcomes among ICU patients when compared with nTTE.

**CONCLUSIONS**

In critically ill, propensity-matched hospitalized patients undergoing echocardiography, cTTE is associated with a 28% lower mortality at 48 h in comparison with patients undergoing nTTE. These results are reassuring, given previous reports suggesting an association between cTTE and increased mortality in critically ill patients.

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**Table 6.** Demographic Data for Critically Ill Patients With 48-h Mortality Data (Matched Dataset, n = 32,434)

<table>
<thead>
<tr>
<th></th>
<th>Died</th>
<th>Ultrasound Contrast Agent Group</th>
<th>Odds Ratio* (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Noncontrast Group (n = 16,217)</td>
<td>Ultrasound Contrast Agent Group (n = 16,217)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–44</td>
<td>45/1,237 (3.64)</td>
<td>23/1,266 (1.82)</td>
<td>0.43 (0.25–0.73)</td>
<td>0.0017</td>
</tr>
<tr>
<td>45–64</td>
<td>167/6,321 (2.64)</td>
<td>109/6,283 (1.73)</td>
<td>0.64 (0.50–0.82)</td>
<td>0.0004</td>
</tr>
<tr>
<td>65–74</td>
<td>129/4,298 (3.00)</td>
<td>80/4,172 (1.92)</td>
<td>0.61 (0.46–0.82)</td>
<td>0.0008</td>
</tr>
<tr>
<td>75–79</td>
<td>53/1,916 (2.77)</td>
<td>63/1,991 (3.16)</td>
<td>1.2 (0.79–1.7)</td>
<td>0.44</td>
</tr>
<tr>
<td>80+</td>
<td>88/2,445 (3.60)</td>
<td>78/2,505 (3.11)</td>
<td>0.85 (0.62–1.2)</td>
<td>0.31</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>65.31 ± 15.09</td>
<td>68.03 ± 14.26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>67 (20–97)</td>
<td>70 (18–97)</td>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>292/10,335 (2.82)</td>
<td>210/10,290 (2.04)</td>
<td>0.70 (0.59–0.84)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>190/5,862 (3.24)</td>
<td>143/5,927 (2.41)</td>
<td>0.73 (0.58–0.91)</td>
<td>0.0050</td>
</tr>
</tbody>
</table>

Values are n/N (%), mean ± SD, or median (range). *Wald model logistic regression adjusted odds ratio. Adjusted odds ratio (Wald).

CI = confidence interval.
REFERENCES


Key Words: contrast echocardiography ■ contrast enhanced ultrasound ■ ultrasound contrast agents.