Perioperative Troponin is a Predictor of Both Short- and Intermediate-term Mortality Among Patients Undergoing Major Urologic Surgery

Yaw A. Nyame, Benjamin Abelson, Abhinav Khanna, Venu Menon, Eric A. Klein, and Howard B. Goldman

OBJECTIVE
To determine whether a positive troponin is a predictor of intermediate- and long-term mortality in patients undergoing major urologic surgeries at our institution.

METHODS
This is a retrospective analysis of patients undergoing major urologic surgery at the Cleveland Clinic from 2010-2015. Patients were stratified by the presence and maximum value of troponin blood-draw, if performed within 30 days of surgery. Survival analysis was performed using Kaplan-Meier function (univariate) and Cox regression analysis (continuous) to assess mortality risk.

RESULTS
Within 30 days of surgery, 1305 (15.5%) patients a troponin drawn, and 304 (3.6%) of them had an abnormal troponin level (>0.01 ng/mL). Patients with positive troponin drawn for cause within 30 days of surgery had a significantly decreased overall survival at 5 years of 70.6% (95% CI 62.6, 77.2) when compared to patients with negative troponin (81.7% [95% CI 77.4, 85.3]) and no troponin drawn (90.4% [95% CI 89.0, 91.6]).

CONCLUSION
For cause serum troponin blood draw and peak levels demonstrated a positive correlation with all-cause mortality in patients undergoing major urologic surgeries. Prospective studies are needed to better understand the utility of postoperative troponin as predictive marker of mortality.

SUBJECTS AND METHODS
This is a retrospective analysis of patients undergoing major urologic surgery from 2010-2015 at a large, academic US medical center (IRB# 15-1606, 12/2015). Data...
was collected by query of the electronic medical record. Patients were included if they were 18 years of age or older at the time of surgery, and had 1 of the following operations by a surgeon in our department during the study period—radical cystectomy, radical prostatectomy, radical or partial nephrectomy, inferior vena cava (IVC) thrombectomy, adrenalectomy, retroperitoneal lymph node dissection, inguinal lymph node dissection, and penile cancer surgery, urinary fistula surgeries, and kidney and/or pancreas transplantation. In total, 8404 patients were identified from our search. Ninety-four patients were excluded from analysis for incomplete data, and a final cohort of 8310 patients was analyzed. Institutional review board approval was obtained for this study.

**Clinical and Demographic Data**

Relevant clinical data including standing height and weight, length of hospital stay, age at surgery, sex, and ethnicity were all obtained from the medical record. Similarly, troponin levels (ng/mL) and timing of blood draw to surgery were recorded for each patient. Troponin blood draws were completed every 8 hours for 24 hours per routine practice at our institution, and the highest level was included in our study. Troponin levels were divided into groups based on cut points established in the literature (<0.01, 0.01-0.029, >0.03). To estimate overall health risk, the Charlson comorbidity index (CCI) was calculated for each patient. Lastly, all relevant follow-up data including last known follow-up, and timing of myocardial infarction (MI) and all-cause mortality were collected.

**Statistical Analysis**

Data are presented as medians with interquartile range (IQR) or proportions. The primary endpoint of this study is ACM. The secondary endpoints of analysis are 30- and 90-day in-hospital mortality. The incidence of each endpoint is reported per 100 person-years or 100 person-days. Each outcome was evaluated using Kaplan-Meier analysis with log-rank testing to determine significance. Adjusted analyses were performed with Cox regressions to calculate hazard ratios. Adjusted models were constructed with the sequential addition of all relevant clinical variables. Variables were kept in the model if \( P < .10 \). Entry into all time-to-event analyses occurred on the date of diagnosis. Patients were censored during analysis when they died or at the end of follow-up. The cumulative survival free from each point was additionally calculated at 3- and 5-years for the cohort. All statistical tests were 2-sided. Statistical significance was defined as \( P < .05 \). All analyses were conducted using Stata 12.1 (StataCorp 2011, College Station, TX).

### RESULTS

Baseline characteristics are shown in Table 1. The median age of the cohort is 60.0 years IQR (52.0-67.0), and 2202 (26.5%) patients were female. The median length of stay following surgery was 3.0 days IQR (2.0-6.0), and median total follow-up of 14.5 months IQR (3.2-36.3). The most common surgeries performed in this study were renal and prostate surgeries, which accounted for 35.9% and 35.8% of all cases, respectively. In total, 1305 (15.7%) patients had a troponin drawn for cause within 30 days of surgery, and 304 (23.3%) of these patients had an abnormal troponin level (>0.01 ng/mL). MI was diagnosed and treated in 40 (0.5%) and 61 (0.7%) within 30 and 90 days of surgery.

#### Primary Endpoint

In total, 451 patients died during the study period; however, 1 patient death was excluded from time to event analysis because it occurred on the day of surgery (Supplemental Table 1). The survival rate was 91.0% and 88.4% at 3- and 5-years, respectively. Patients with any troponin drawn within 30 days of surgery had a significantly

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Continuous, Median (IQR)</th>
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</thead>
<tbody>
<tr>
<td>Age at surgery, years</td>
<td>60.0 (52.0-67.0)</td>
</tr>
<tr>
<td>Year of surgery</td>
<td>2012 (2011-2014)</td>
</tr>
<tr>
<td>Follow-up, months</td>
<td>14.5 (3.2-36.3)</td>
</tr>
<tr>
<td>Body mass index, kg/m² (n = 8301)</td>
<td>28.3 (25.3-32.1)</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>3.0 (2.0-6.0)</td>
</tr>
<tr>
<td>Length of stay, days (n = 8116)</td>
<td>3.0 (2.0-6.0)</td>
</tr>
<tr>
<td>Max troponin level, ng/mL (n = 1305)</td>
<td>0.0 (0.00-0.0)</td>
</tr>
<tr>
<td>Time from surgery to troponin blood draw, days (n = 1305)</td>
<td>1.0 (1.0-4.0)</td>
</tr>
<tr>
<td>Time from surgery to mortality, months (n = 451)</td>
<td>10.6 (4.5-22.9)</td>
</tr>
</tbody>
</table>

### Table 1. Demographic and clinical characteristics of patients undergoing major urologic surgery at the Cleveland Clinic from 2010-2015 (n = 8310)

**Categorical, n (%)**

- Obese, yes (n = 8301): 3126 (37.7)
- Male, yes: 6108 (73.5)
- European American: 7059 (84.9)
- Declined: 118 (1.4)
- All-cause mortality, yes: 451 (5.4)
- 30 day in-hospital mortality, yes: 34 (0.4)
- 90 day in-hospital mortality, yes: 79 (0.9)
- Myocardial infarction within 30 days of surgery, yes: 40 (0.5)
- Myocardial infarction within 90 days of surgery, yes: 61 (0.7)

**Continuous, Median (IQR)**

- Body-mass-index, kg/m² (n = 8301): 28.3 (25.3-32.1)
- Length of stay, days (n = 8116): 3.0 (2.0-6.0)
- Max troponin level, ng/mL (n = 1305): 0.0 (0.00-0.0)
- Time from surgery to troponin blood draw, days (n = 1305): 1.0 (1.0-4.0)
- Time from surgery to mortality, months (n = 451): 10.6 (4.5-22.9)
increased risk of mortality at 5 years, with mortality risk positively correlating with peak troponin levels (Fig. 1, \(P < .0001\)). In fact, when stratified by no troponin draw, negative troponin draw, and positive troponin draw the cumulative rate of survival at 5-years was 90.4%, 81.7%, and 70.6%, respectively (Supplemental Table 2). On adjusted model controlling for age, CCI, ethnicity, year of surgery, and length of stay, both troponin < 0.01 ng/ml and troponin \(\geq 0.01\) ng/mL were associated with an increased risk of mortality compared to no troponin draw with hazard ratio of 1.48 (95% CI 1.17, 1.87; \(P = .001\)) and 1.86 (95% CI 1.36, 2.54; \(P < .001\)), respectively (Table 2).

Secondary Endpoint
Thirty-three and 77 patients experienced in-hospital death at 30- and 90-days, respectively. The cumulative incidence of in-hospital mortality was 0.014 and 0.012 per 100 person-days at 30- and 90-days. A positive for-cause troponin level demonstrated a strong correlation with in-hospital mortality at 30 days on adjusted analysis with a hazard ratio of 9.2 (95% CI 3.86, 21.9; \(P < .001\)) when compared to no troponin blood draw postoperatively (Supplemental Table 3). The risk of 30-day mortality in patients with positive troponin was most significant with those with peak troponin \(\geq 0.03\) ng/mL demonstrating a hazard ratio of 10.6 (95% CI 4.30, 26.0; \(P < .001\)) compared to patients who did not have a troponin drawn postoperatively (Supplemental Table 3). The rate of MI also increased with increasing peak troponin levels following surgery (\(P < .001\); Supplemental Figure 1). Thirty-seven percent of patients underwent radical prostatectomy and 21.8% underwent partial nephrectomy (see Supplemental Table 4 for additional surgery categories).

**DISCUSSION**
Postoperative mortality in patients undergoing noncardiac surgery is a significant cause of death worldwide, and recent prospective data from the international, multi-institutional VISION and MINS trials have demonstrated that peak troponin after noncardiac surgery is a strong predictor of mortality.\(^1\) However, to our knowledge, there is no data describing the impact of peak troponin levels in patients undergoing urologic surgeries. In our single institution analysis, we found that patients who have troponin drawn for-cause demonstrate a significantly increased risk of mortality with short and intermediate term follow-up. Specifically, patients who had peak troponin levels greater than 0.03 demonstrated a 91% and 960% increased risk of mortality at 5 years and 30 days, respectively. Surprisingly, even patients who had a negative for-cause troponin draw had higher mortality than those who did not have a troponin checked. These outcomes were noted with median follow-up of 14.5 months in 8310 patients treated at our institution from 2010-2015.

**Table 2.** Univariate and multivariate Cox regression analysis of all-cause mortality for patients undergoing major urological surgery at the Cleveland Clinic from 2010-2015

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate HR (95% CI)</th>
<th>(P) Value</th>
<th>Multivariate(^a) HR (95% CI)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at surgery, ng/ml</td>
<td>1.05 (1.04, 1.06)</td>
<td>&lt;.001</td>
<td>1.04 (1.03, 1.05)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>1.18 (1.16, 1.21)</td>
<td>&lt;.001</td>
<td>1.15 (1.12, 1.17)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>European American</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>0.70 (0.52, 0.96)</td>
<td>.03</td>
<td>0.63 (0.46, 0.87)</td>
<td>.004</td>
</tr>
<tr>
<td>Other</td>
<td>0.3 (0.10, 0.96)</td>
<td>.04</td>
<td>0.28 (0.09, 0.87)</td>
<td>.03</td>
</tr>
<tr>
<td>Declined</td>
<td>1.22 (0.54, 2.73)</td>
<td>.63</td>
<td>1.23 (0.55, 2.76)</td>
<td>.62</td>
</tr>
<tr>
<td>Length of stay, days</td>
<td>1.06 (1.06, 1.07)</td>
<td>&lt;.001</td>
<td>1.04 (1.04, 1.05)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Year of surgery</td>
<td>0.93 (0.87, 0.99)</td>
<td>.047</td>
<td>0.93 (0.87, 0.99)</td>
<td>.04</td>
</tr>
<tr>
<td>Postoperative troponin level, ng/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Troponins</td>
<td>Reference</td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>&lt; 0.01</td>
<td>2.40 (1.91, 3.01)</td>
<td>&lt;.001</td>
<td>1.48 (1.17, 1.87)</td>
<td>.001</td>
</tr>
<tr>
<td>(\geq 0.01)</td>
<td>4.54 (3.43, 6.01)</td>
<td>&lt;.001</td>
<td>1.86 (1.36, 2.54)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

\(^a\)Multivariate analysis contains 8091 patients due to missing length of stay data on 194 patients or 37 patients not having sufficient follow-up for survival analysis (total 219 patients). Variables with \(P > .10\) were excluded from the final model and included sex and body-mass-index (continuous and categorical).
The VISION and MINS study focused on 2 aspects of perioperative troponin, which were the impact of screening and short-term mortality. Conversely, this retrospective analysis looked at longer term in-hospital mortality, and troponin levels in this cohort were drawn for cause (ie, postoperative cardiopulmonary symptoms or screening trials such as VISION). These distinctions are very important, and limit the applicability of the conclusions that should be drawn from mortality risk among patients in our cohort. Nonetheless our findings show that troponins, drawn for cause, are a strong predictor of both short- and long-term mortality. The 5-year cumulative survival rate was lowest in patients with positive troponins (defined as peak ≥ 0.01) at 70.6% (95% CI 62.6, 77.2) compared to no troponin draw 90.6% (95% CI 89.0, 91.6). And this increased risk of mortality remained significantly different in our patients, even when adjusted for comorbid conditions measure by CCI, age, and ethnicity. However, it must be acknowledged that there is a selection bias in favor of higher mortality in patients with active cardiopulmonary symptoms or a change in clinical status that motivates a provider to order troponin evaluation.

Interestingly, patients with negative troponins after urologic surgery demonstrated an increased risk of long-term mortality compared to patients who did not have a troponin drawn after surgery. This association was only observed at longer follow-up, and a negative troponin did not demonstrate any association with 30 in-hospital mortalities (Supplemental Table 3). This observation may shed light on the reasons that a provider may order a troponin blood draw in a postoperative patient, although our study was not designed to evaluate such clinical decision-making. Troponin is usually ordered as part of an evaluation for a specific cardiopulmonary symptom like chest pain or shortness of breath, or it may be included in a workup for less specific signs like hypotension, altered mental status, or arrhythmias. Perhaps a provider is more likely to order a troponin measurement in a patient with a history of cardiovascular disease, which itself is a risk factor for perioperative morbidity and mortality. Nevertheless, given the increased mortality among patients with negative troponin measurements, any patient with cardiopulmonary symptoms following surgery may benefit from closer postoperative risk management.

Lastly, the MINS trial demonstrated that 65% of patients with positive screening troponins following surgery are completely asymptomatic. The study also demonstrated that 9% of patients who were screened had positive troponins. Given the strong association between for-cause troponin and mortality demonstrated in this study with mortality, we have used this baseline data to advocate for a prospective screening trial, which is now approaching its first year of follow-up. In our protocol, all patients over the age of 45 undergoing major urologic surgeries have a screening troponin test drawn on postoperative day 1-3. A troponin ≥ 0.01 prompts cardiology consult, in addition to electrocardiogram. Patients who do not have evidence of myocardial infarct at surgery are given the diagnosis of MINS, and have outpatient follow-up arranged. We look forward to sharing the results of this trial in the future; however, we recognize that there are no proven interventions that exist to decrease mortality of patients identified as at-risk for mortality after noncardiac surgeries. Nevertheless, in certain patients, surgery may serve as a “stress-test” that reveals either underlying disease that necessitates further evaluation or intervention (ie, echocardiogram, cardiac catheterization, or revascularization), or modifiable risk factors that could be managed.

There are several limitations to this trial. First, the retrospective nature of this study has inherent selection biases. Specifically, the patients with troponin blood draw are at higher risk for cardiac events based on the postoperative symptoms such as chest pain, arrhythmia, or a change in clinical status which prompted a troponin blood draw. Second, in-hospital mortality only represents 80% of mortality following surgery and it is possible that events that occurred are not accounted for in this cohort. Nonetheless, this is a unique study of a cheap ($4 at our institution) and routine blood test that demonstrates the capability to identify patients at risk for mortality after urologic surgeries. Lastly, increased mortality among those patients with elevated troponin may be confounded by a delay in adjuvant oncologic therapies due to cardiovascular workup or treatment. However, given that a small minority of the malignancies treated in our field, routinely warrant adjuvant therapies, this is not likely to significantly skew the results.

In conclusion, postoperative peak troponin concentration drawn for-cause demonstrated a significant association with both short- and long-term mortality in patients undergoing major urologic surgeries. Furthermore, even patients with a negative postoperative troponin demonstrated a significant increase in mortality. These findings, along with evidence from several other surgical specialties, represent a significant opportunity for urologists and other members of the healthcare team to identify patients at increased risk for postoperative mortality, and to intervene upon any identifiable and modifiable risk factors in urologic patients. Further prospective investigation, which is ongoing at our institution, is needed to determine whether perioperative troponin screening can reduce mortality risk.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.urology.2018.06.060.

References
diagnostic criteria, characteristics, predictors, and 30-day outcomes. Anesthesiology. 2014;120:564–578.


Editorial Comment

Surgery plays a fundamental role in the care of millions of patients worldwide, each year.1,2 Unfortunately, cardiovascular events occurring after surgery remain as one of the leading cause of morbidity and mortality after major non-cardiac surgery. The results of several large studies demonstrate that a higher than “normal” postoperative troponin concentrations in the absence of a clinical diagnosis of myocardial infarct (also known as myocardial injury after non-cardiac surgery, MINS) is an independent risk factor of short and long term morbidity and mortality.3–6

In this issue of the journal, Nyame et al. elegantly demonstrated in a large cohort of urological patients (n = 8,310) who underwent non-cardiac surgery that those subjects who had abnormal postoperative (30 days) troponin levels (3.6%) also had a significantly worse 5 years overall survival (70.6%) than those individuals with normal troponin concentrations (81.7%) and patients in whom troponins were not measured (90.4%). In my opinion, the reader should carefully consider that the cohort of patients involved in Nyame’s study represents a predominantly cancer population of patients in whom troponin levels were not routinely measured after surgery but as a result of changes in the patients’ medical conditions. In that regards, Nyame’s study studies’ patients significantly differ from subjects in the VISION trial in whom troponins were routinely measured postoperatively and in 8% of them MINS was detected. This fact does not underscore the relevance of Nyame et al. findings, but again it indicates that routine testing appears appropriate. I think that it is also important to consider that the authors of the manuscript published in this issue of the journal did not provide data on preoperative troponin values which can be increased in up to 40% of the patients undergoing major non-cardiac surgery.7–8 The relevance of an abnormal preoperative troponin resides in the fact that the risk of postoperative mortality is two-folds or higher than in patients with normal troponin concentrations.7

The treatment of patients with postoperative troponin elevations appears to be indicated. In the MANAGE trial, patients with MINS who were allocated to receive dabigatran had fewer major vascular than complications than those treated with placebo (hazard ratio: 0.72, 95% confidence interval: 0.55–0.93; P = 0.0115). It is worth considering that not every postoperative elevation in troponin is due to myocardial ischemia (ie, sepsis, pulmonary embolism, myocarditis, or cardioversion). Therefore, it is not clear if patients all with postoperative troponin elevations in Nyame’s study would have benefited from cardiovascular “optimized medical therapy” or dabigatran.

The findings of the study by Nyame et al. gives an insight on the long-term prognostic value of abnormal postoperative troponin measurements. They also open an opportunity to discover new biomarkers or more sensitive techniques (high sensitivity troponin assays) to detect small changes in troponins that could be used in patients “normal” troponins.

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References


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Author Reply

If it were tracked by the CDC, mortality after non-cardiac surgery would rank among the top 4 causes of mortality in the United States.1 The aim of our study was to assess the association between postoperative troponin levels, and both short- and intermediate- term mortality in urologic patients undergoing major operations. This baseline information was needed as background information for a quality project to assess the role of routine troponin screening in our department. As such, there are a few inherent biases that were pointed out in this excellent
editorial highlighting the role that troponins may play as a biomarker to predict mortality in our surgical patients.

We certainly have a selection bias towards oncologic patients, which is a reflection of the case mix at our institution and the author’s decision to select the patient who underwent major urologic surgeries. To address for confounding influence of this selection bias, we controlled for both age and comorbidity in our multivariate analysis. It is also important to note that this high risk population is who we wanted to screen at our institution, as they possessed the most probable opportunity for successful intervention.

The editorial also highlights an important distinction of our study from the VISION and myocardial injury after non-cardiac surgery (MINS) trials, which is that our troponins were drawn for cause following surgery. This means that the patients had troponin levels drawn for either an overt cardiopulmonary symptom or a diagnostic abnormality such as an arrhythmia on telemetry. Roughly 16% of the patients we selected during our study period had a positive troponin, and it is unclear how troponin blood draws from asymptomatic patients in our cohort would alter our findings.

The role of troponin as a biomarker for predicting mortality in urologic patients is interesting. Almassi and colleagues demonstrated that current procedures for assessing preoperative cardiac risk often lead to unnecessary referrals and diagnostic testing with little impact on patient outcomes. More data is needed to understand how preoperative troponin screening can be used to better risk stratify cardiovascular health beyond the American College of Cardiology risk strata in patients undergoing urologic procedures. Unfortunately, we do not perform preoperative screening at our institution and did not include them in our prospective cohort study.

Lastly, it is unclear how to utilize the results of a positive screening troponin. Although the MANAGE trial showed a reduction in major vascular complications after non-cardiac surgery in patients placed on anticoagulation; the POISE trial demonstrated no benefit to anti-platelet therapy in reducing mortality in patients undergoing major non-cardiac surgery. In our own institutional practice, we chose to simply initiate a referral to cardiology in the form of an inpatient consult. We have completed the one-year screening trial in our department and look forward to sharing our results with the urologic community later this year.

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References

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