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Renal Dysfunction Influences the Diagnostic and Prognostic Performance of High-Sensitivity Cardiac Troponin I

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ABSTRACT

Measures of cardiac troponin (cTn) may have lower specificity for myocardial infarction in patients with CKD. We examined the diagnostic accuracy of baseline and serial high-sensitivity cTnI (hs-cTnI) measurements for myocardial infarction and 30- and 180-day mortality according to renal function. hs-cTnI was measured (Abbott assay) using sex-specific 99th percentiles (women, 16 ng/L; men, 34 ng/L) in 1555 adults presenting to the emergency department with symptoms suggesting ischemia (NCT02060760). Myocardial infarction was adjudicated along universal definition classification. Renal function did not significantly affect sensitivity or negative predictive values. Specificity decreased with impaired renal function from 93%–95% with normal function (eGFR$\geq$90 ml/min per 1.73 m^2; *n*=722) to 57%–61% with severely impaired renal function (eGFR$<$30 ml/min per 1.73 m^2; *n*=81) and 40%–41% on dialysis (*n*=78). Positive predictive values decreased with decreasing renal function from 51%–57% with normal function to 27%–42% with severely impaired function and 15%–32% on dialysis. Receiver operating characteristic curve areas trended lower at baseline and 3 hours with renal impairment. Mortality increased significantly with increasing hs-cTnI tertile (1.3%, 6.0%, and 10.4%, respectively). Patients with hs-cTnI concentration exceeding concentrations in the 99th percentiles had a mortality rate (11.7%) significantly higher than that of patients with concentrations between 99th percentile concentrations and limit of detection (6.2%) or below limit of detection (1.1%). Renal dysfunction and dialysis reduced the rule-in performance but not the rule-out performance of hs-cTnI for myocardial infarction, and mortality increased in patients with higher hs-cTnI concentrations and any level of renal dysfunction.

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Cardiac troponin I (cTnI) and cardiac troponin T (cTnT) are sensitive biomarkers of myocardial injury, and they are routinely used to diagnose acute myocardial infarction (MI).[1–4] Although cardiac troponin (cTn) testing is highly specific for myocardial injury, multiple disease states in addition to MI can lead to myocardial injury and cTn increases above the 99th percentile, including CKD.[1–8] Patients with CKD can have increased cTn concentrations in the absence of MI,[8] a finding that has been postulated to be caused by chronic structural heart disease rather than acute injury.[5,6] One misconception by clinicians is that increased cTn concentrations in renal impaired patients are due to impaired renal elimination of cTn, a mechanism

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that has not been proven to date for cTnI but for cTnT, seems to be influenced by kidney function.[9,10] A recent review described widely varying estimates of cTn diagnostic performance in the setting of CKD.[5] Therefore, cTn testing may be expected to show lower clinical specificity for MI in the setting of CKD.[5,7,11–13] Direct comparison with performance criteria reported in non-CKD populations is difficult due to the lack of consistency used for diagnostic cutoff concentrations and other population parameters between studies. Understanding the diagnostic performance of cTn testing in the setting of CKD is important for clinicians given that patients with CKD are at higher risk of developing cardiovascular disease than the general population and that cardiovascular disease is the leading cause of death in those patients with ESRD.[14,15] Patients with eGFR<45 are three times as likely to present with acute MI as with stable angina as the initial manifestation of ischemic heart disease.[15]

Studies carried out over the past approximately 15 years have focused primarily on the prognostic rather than diagnostic performance of cTn testing in the setting of CKD.[5] The literature shows the prognostic value of cTn testing in patients with CKD both with and without underlying acute coronary syndrome, showing that increased cTnI and cTnT concentrations are associated with greater risk of death and cardiac events in patients with renal disease than in those with normal renal function.[6,11–13,16,17] Assessments of the diagnostic performance of cTn assays with renal impairment are less common, especially those addressing the more novel high-sensitivity assays that are increasingly used worldwide.[18] Two studies have shown that the diagnostic accuracy of high-sensitivity cardiac troponin T (hs-cTnT) for MI was significantly reduced in patients with renal dysfunction versus those with normal renal function.[19,20]

In this study, our goals were threefold in patients presenting to the emergency department with symptoms suggestive of ischemia. First, we examined the diagnostic accuracy of baseline and serial high-sensitivity cardiac troponin I (hs-cTnI) measurements for MI according to varying renal function. Second, we compared diagnostic accuracies between hs-cTnI and contemporary cTnI assays. Third, we examined 180-day all-cause mortality with respect to varying renal function.

RESULTS

A total of 1555 patients presenting to the emergency department met inclusion criteria. Table 1 shows the demographics and clinical characteristics of our study population. Acute MI occurred in 167 (10.7%) patients, including 66 (4.2%) type 1 MIs and 101 (6.5%) type 2 MIs. MI by each eGFR patient group was as follows: normal renal function, *n*=49 (6.8%); mildly impaired renal function, *n*=50 (11.2%); moderately impaired renal function, *n*=41 (17.9%); severely impaired renal function, *n*=17 (21.0%); and on dialysis, *n*=10 (12.8%). Mean (SD) eGFRs for the normal (*n*=722; 46.4%), mildly impaired (*n*=445; 28.6%), moderately impaired (*n*=229; 14.7%), and severely impaired (*n*=81; 5.2%) groups were 119 (28), 76 (8), 47 (8), and 17 (7) ml/min per 1.73 m^2, respectively.

Significance Statement

Cardiac troponin is a sensitive biomarker of myocardial injury, routinely used to diagnose acute myocardial infarction (MI), but troponin assays are of reduced utility for MI diagnosis in patients with impaired renal function. The authors examined diagnostic performance of contemporary and high-sensitivity cardiac troponin (hs-cTnI) measurements in a large cohort of patients presenting with symptoms suggestive of MI. hs-cTnI had excellent diagnostic accuracy, but clinical specificity and positive predictive value for ruling in MI trended downward with decreasing renal function. In contrast, the assay's sensitivity and negative predictive value for ruling out showed no significant dependence on renal function. The results support developing strategies for implementation of high-sensitivity troponin assays for early rule out and rule in of MI in patients with renal dysfunction.

Clinical sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for hs-cTnI assays for all times and patient groups are shown in Table 2. Corresponding results obtained using the contemporary cTnI assay are shown in Supplemental Table 1. For all patients but those on dialysis, hs-cTnI sensitivities within each group substantially increased from baseline to ≥91% at 3 hours. However, it was not until 6 hours that sensitivities increased above 90% and approached 100% in the dialysis group. In comparison, contemporary cTnI sensitivities were ≤90% at 6–9 hours, except for in the dialysis group. NPV was relatively stable across renal function groups, with all showing at least one time >98% by 6 hours. The specificity of the hs-cTnI assay decreased with worsening renal function. Specificity ranged from 93.1% to 95.3% in the normal renal function group, from 83.5% to 87.6% in the mildly impaired renal function group, from 67.5% to 78.7% in the moderately impaired renal function group, from 56.8% to 60.9% in the severely impaired renal function group, and from 39.7% to 41.0% in the dialysis group. There were no substantial differences between time points within each group. The PPV of the hs-cTnI assay also decreased with decreasing renal function. PPVs ranged from 50.8% to 56.9% in the normal renal function group, from 38.8% to 57.4% in the mildly impaired renal function group, from 34.4% to 50.0% in the moderately impaired renal function group, from 26.9% to 41.9% in the severely impaired renal function group, and from 14.6% to 32.1% in the dialysis group. Sensitivity, specificity, PPV, and NPV calculated using cumulative diagnostic estimates over 0–3 hours were similar to those calculated at 3 hours. Receiver operating characteristic (ROC) curve areas (95% confidence intervals [95% CIs]) trended lower at both baseline and 3 hours with renal impairment and dialysis, with the 3-hour value showing improved diagnostic accuracy: baseline normal: 0.85 (95% CI, 0.79 to 0.92); baseline mild: 0.75 (95% CI, 0.68 to 0.82); baseline moderate: 0.65 (95% CI, 0.57 to 0.73); baseline severe: 0.78 (95% CI, 0.69 to 0.86); baseline dialysis: 0.55 (95% CI, 0.39 to

Table 1. Demographic and clinical characteristics of 1555 patients in the study cohort

Patient Clinical Characteristics	All	Normal: eGFR≥90	Mildly Impaired: eGFR≥60 to <90	Moderately Impaired: eGFR≥30 to <60	Severely Impaired: eGFR<30	On Dialysis	*P* Value
N	1555	722	445	229	81	78	
Age, mean (SD)	58 (15)	52 (14)	61 (14)	68 (15)	63 (13)	58 (13)	<0.001
MI at presentation, high sensitivity, *n* (%)	167 (11)	49 (7)	50 (11)	41 (18)	17 (21)	10 (13)	<0.001
MI at presentation, contemporary, *n* (%)	205 (13)	72 (10)	61 (14)	46 (20)	14 (17)	12 (15)	0.001
Sex, *n* (%)							<0.001
Men	881 (57)	455 (63)	236 (53)	104 (45)	43 (53)	43 (55)	
Women	674 (43)	267 (37)	209 (47)	125 (55)	38 (47)	35 (45)	
Race, *n* (%)							<0.001
White	669 (43)	278 (39)	235 (53)	113 (49)	29 (36)	14 (18)	
Black	668 (43)	332 (46)	166 (37)	86 (38)	37 (46)	47 (60)	
Native American	84 (5)	48 (7)	13 (3)	10 (4)	8 (10)	5 (6)	
Asian	46 (3)	19 (3)	11 (2)	8 (3)	5 (6)	3 (4)	
Other	88 (6)	45 (6)	20 (4)	12 (5)	2 (2)	9 (12)	
Medical history, *n* (%)							
Hypertension	1032 (66)	406 (56)	297 (67)	189 (83)	70 (86)	70 (90)	<0.001
Diabetes	486 (31)	201 (28)	117 (26)	86 (38)	47 (58)	35 (45)	<0.001
Current smoker	567 (36)	322 (45)	150 (34)	54 (24)	17 (21)	24 (31)	<0.001
Dyslipidemia	670 (43)	245 (34)	205 (46)	137 (60)	49 (60)	34 (44)	<0.001
Drug use	205 (13)	105 (15)	54 (12)	25 (11)	6 (7)	15 (19)	0.11
Previous acute MI	184 (12)	72 (10)	49 (11)	41 (18)	12 (15)	10 (13)	0.02
Coronary artery disease	259 (17)	85 (12)	79 (18)	59 (26)	22 (27)	14 (18)	<0.001
Previous cardiac arrest	20 (1)	5 (1)	7 (2)	6 (3)	0 (0)	2 (3)	0.11
Previous PCI or stent	153 (10)	55 (8)	47 (11)	38 (17)	9 (11)	4 (5)	0.001
Heart failure	224 (14)	56 (8)	58 (13)	62 (27)	25 (31)	23 (29)	<0.001
Atrial fibrillation	126 (8)	31 (4)	42 (9)	34 (15)	10 (12)	9 (12)	<0.001
Previous CABG	72 (5)	26 (4)	17 (4)	17 (7)	7 (9)	5 (6)	0.04
Peripheral vascular disease	41 (3)	11 (2)	16 (4)	8 (3)	5 (6)	1 (1)	0.04
Previous stroke	147 (9)	42 (6)	53 (12)	33 (14)	10 (12)	9 (12)	<0.001
Pace maker	86 (6)	20 (3)	27 (6)	27 (12)	7 (9)	5 (6)	<0.001
Body mass index	30 (9)	30 (10)	30 (8)	29 (9)	31 (10)	28 (10)	0.10
Symptoms, *n* (%)							
Chest discomfort	442 (28)	256 (35)	120 (27)	35 (15)	16 (20)	15 (19)	<0.001
Arm or shoulder discomfort	226 (15)	128 (18)	71 (16)	16 (7)	6 (7)	5 (6)	<0.001
Jaw or neck discomfort	92 (6)	47 (7)	27 (6)	12 (5)	4 (5)	2 (3)	0.67
Epigastric discomfort	87 (6)	50 (7)	19 (4)	9 (4)	5 (6)	4 (5)	0.27
Nausea or vomiting	365 (23)	195 (27)	93 (21)	44 (19)	21 (26)	12 (15)	0.02
Dyspnea	644 (41)	295 (41)	183 (41)	94 (41)	34 (42)	38 (49)	0.76
Fatigue	77 (5)	26 (4)	18 (4)	21 (9)	7 (9)	5 (6)	<0.01
Diaphoresis	156 (10)	89 (12)	45 (10)	17 (7)	3 (4)	2 (3)	<0.01
Laboratory values, mean (SD)							
NT-proBNP, ng/L	3064 (7213)	955 (1775)	1533 (2416)	4247 (8979)	9679 (13,170)	18,303 (13,707)	<0.001
eGFR, ml/min per 1.73 m^2	85 (41)	119 (28)	76 (8)	47 (8)	17 (7)	10 (13)	<0.001
Hemoglobin, g/dl	13 (2)	13 (2)	13 (2)	12 (2)	11 (3)	10 (2)	<0.001
Baseline hs-cTnI, ng/L	79 (1169)	96 (1642)	41 (204)	61 (346)	209 (1263)	62 (166)	0.79
Maximum hs-cTnI, ng/L	368 (2933)	359 (3299)	198 (1266)	621 (3858)	833 (3980)	196 (1149)	0.24
Baseline contemporary cTnI, μg/L	0.09 (1.29)	0.11 (1.82)	0.05 (0.23)	0.07 (0.28)	0.26 (1.49)	0.07 (0.15)	0.73
Maximum contemporary cTnI, μg/L	0.42 (3.60)	0.45 (4.17)	0.19 (1.01)	0.73 (5.10)	0.80 (3.56)	0.18 (0.91)	0.30

Normal: eGFR≥90 ml/min per 1.73 m^2; mildly impaired: eGFR≥60 to <90 ml/min per 1.73 m^2; moderately impaired: eGFR≥30 to <60 ml/min per 1.73 m^2; severely impaired: eGFR≤30 ml/min per 1.73 m^2. PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; NT-proBNP, N-terminal pro B-type natiuretic peptide.

0.71); 3-hour normal: 0.92 (95% CI, 0.87 to 0.97); 3-hour mild: 0.90 (95% CI, 0.85 to 0.95); 3-hour moderate: 0.87 (95% CI, 0.82 to 0.92); 3-hour severe: 0.79 (95% CI, 0.71 to 0.87); and 3-hour dialysis: 0.63 (95% CI, 0.47 to 0.79).

The 180-day mortality with respect to hs-cTnI by tertile (0–2.5 ng/ml [tertile 1; *n*=546], 2.5–10.6 ng/L [tertile 2; *n*=555], and >10.6 ng/L (tertile 3; *n*=539]) for all patients is shown in Figure 1. Mortality increased significantly with increasing

Table 2. Sensitivity, specificity, PPV, and NPV with respect to eGFR and dialysis treatment status over 24 hours after presentation for hs-cTnI assay

Renal Function	*n*	Sensitivity, %	Specificity, %	PPV, %	NPV, %
Normal					
Baseline	722	75.5 (63.5 to 87.6)	95.3 (93.6 to 96.9)	53.6 (41.9 to 65.4)	98.2 (97.1 to 99.2)
3 h	501	91.2 (81.6 to 100.0)	93.6 (91.4 to 95.8)	50.8 (38.3 to 63.4)	99.3 (98.6 to 100.0)
6 h	499	94.3 (86.6 to 100.0)	93.1 (90.8 to 95.4)	50.8 (38.6 to 62.9)	99.5 (98.9 to 100.0)
9 h	421	94.3 (86.6 to 100.0)	93.5 (91.1 to 96.0)	56.9 (44.2 to 69.6)	99.5 (98.7 to 100.0)
0/3 h	501	94.1 (86.2 to 100.0)	92.9 (90.6 to 95.3)	49.2 (37.1 to 61.4)	99.5 (98.9 to 100.0)
Mildly impaired					
Baseline	445	62.0 (48.6 to 75.5)	87.6 (84.3 to 90.9)	38.8 (28.1 to 49.4)	94.8 (92.5 97.1)
3 h	280	93.3 (84.4 to 100.0)	86.4 (82.2 to 90.7)	45.2 (32.8 to 57.6)	99.1 (97.8 to 100.0)
6 h	291	94.6 (87.3 to 100.0)	83.5 (78.9 to 88.0)	45.5 (34.3 to 56.6)	99.1 (97.8 to 100.0)
9 h	259	92.9 (85.1 to 100.0)	86.7 (82.1 to 91.2)	57.4 (45.6 to 69.1)	98.4 (96.7 to 100.0)
0/3 h	280	93.3 (84.4 to 100.0)	86.0 (81.7 to 90.3)	44.4 (32.2 to 56.7)	99.1 (97.8 to 100.0)
Moderately impaired					
Baseline	229	51.2 (35.9 to 66.5)	78.7 (72.9 to 84.6)	34.4 (22.5 to 46.4)	88.1 (83.2 to 93.0)
3 h	147	96.4 (89.6 to 100.0)	77.3 (69.8 to 84.8)	50.0 (36.7 to 63.3)	98.9 (96.8 to 100.0)
6 h	151	87.1 (75.3 to 98.9)	71.7 (63.6 to 79.7)	44.3 (31.8 to 56.7)	95.6 (91.3 to 99.8)
9 h	149	96.9 (90.9 to 100.0)	67.5 (59.0 to 76.0)	44.9 (33.2 to 56.7)	98.8 (96.3 to 100.0)
0/3 h	147	96.4 (89.6 to 100.0)	76.5 (68.9 to 84.1)	49.1 (35.9 to 62.3)	98.9 (96.8 to 100.0)
Severely impaired					
Baseline	81	94.1 (82.9 to 100.0)	60.9 (49.0 to 72.9)	39.0 (24.1 to 54.0)	97.5 (92.7 to 100.0)
3 h	46	100.0 (63.1 to 100.0)	57.9 (42.2 to 73.6)	33.3 (14.5 to 52.2)	100.0 (84.6 to 100.0)
6 h	57	100.0 (75.3 to 100.0)	59.1 (44.6 to 73.6)	41.9 (24.6 to 59.3)	100.0 (86.8 100.0)
9 h	51	100.0 (59.0 to 100.0)	56.8 (42.2 to 71.5)	26.9 (9.9 to 44.0)	100.0 (86.3 to 100.0)
0/3 h	46	100.0 (63.1 to 100.0)	57.9 (42.2 to 73.6)	33.3 (14.5 to 52.2)	100.0 (84.6 to 100.0)
Dialysis					
Baseline	78	70.0 (41.6 to 98.4)	39.7 (28.1 to 51.3)	14.6 (4.6 to 24.6)	90.0 (79.3 to 100.0)
3 h	46	85.7 (59.8 to 100.0)	41.0 (25.6 to 56.5)	20.7 (6.0 to 35.4)	94.1 (82.9 to 100.0)
6 h	57	100.0 (63.1 to 100.0)	40.8 (27.1 to 54.6)	21.6 (8.4 to 34.9)	100.0 (83.2 to 100.0)
9 h	42	90.0 (71.4 to 100.0)	40.6 (23.6 to 57.6)	32.1 (14.8 to 49.4)	92.9 (79.4 to 100.0)
0/3 h	46	100.0 (59.0 to 100.0)	41.0 (25.6 to 56.5)	23.3 (8.2 to 38.5)	100.0 (79.4 to 100.0)

The 95% CIs are shown in parentheses. Normal: eGFR≥90 ml/min per 1.73 m^2; mildly impaired: eGFR≥60 to <90 ml/min per 1.73 m^2; moderately impaired: eGFR≥30 to <60 ml/min per 1.73 m^2; severely impaired: eGFR≤30 ml/min per 1.73 m^2.

hs-cTnI tertile: 1.3% (seven patients), 6.0% (33 patients), and 10.4% (56 patients), respectively ($P<0.001$ for tertile 1 versus 2 and tertile 1 versus 3 and $P<0.01$ for tertile 2 versus 3). The 180-day mortality with respect to hs-cTnI groups defined by concentrations less than limit of detection (LoD; $n=445$), LoD to less than sex-specific upper reference limits (URLs; $n=886$), and greater then sex-specific URLs ($n=309$) is shown in Figure 2. Compared with patients with hs-cTnT concentrations less than LoD, patients with measurable hs-cTnI concentrations between the LoD and the 99th percentile had higher mortality (1.1% [$n=5$] versus 6.2% [$n=55$]; $P<0.001$) and concentrations above the 99th percentile (1.1% [$n=5$] versus 11.7% [$n=36$]; $P<0.001$). Similarly, compared with patients with measurable concentrations between the LoD and the 99th percentile, patients with concentrations above the 99th percentile had a higher mortality (6.2% [$n=55$] versus 11.7% [$n=36$]; $P=0.002$).

Mortality was also assessed with respect to renal function independent of hs-cTnI as shown in Figure 3. Mortality rates at 30 days were 0.8% (six of 722 patients; eGFR≥90 ml/min per 1.73 m^2), 1.6% (seven of 445 patients; eGFR≥60 to <90 ml/min per 1.73 m^2), 7.0% (16 of 229 patients; eGFR≥30 to <60 ml/min per 1.73 m^2), 9.9% (eight of 81 patients; eGFR<30 ml/min per 1.73 m^2), and 5.1% (four of 78 patients on dialysis); P value was <0.001 between the eGFR≥90 ml/min per 1.73 m^2 group and all other groups. Mortality rates at 180 days were 2.5% (18 of 722 patients; eGFR≥90 ml/min per 1.73 m^2), 5.2% (23 of 445 patients; eGFR≥60 to <90 ml/min per 1.73 m^2), 12.7% (29 of 229 patients; eGFR≥30 to <60 ml/min per 1.73 m^2), 14.8% (12 of 81 patients; eGFR<30 ml/min per 1.73 m^2), and 14.1% (11 of 78 patients on dialysis); P value was <0.001 between the eGFR≥90 ml/min per 1.73 m^2 group and all other groups.

Hazard ratios (HRs) and 95% CIs at 180 days increased with decreasing renal function after adjustment for baseline troponin tertiles: HR, 1.62; 95% CI, 0.86 to 3.05 for the mildly impaired renal function group; HR, 3.92; 95% CI, 2.15 to 7.16 for the moderately impaired renal function group; HR, 3.86; 95% CI, 1.80 to 8.25 for the severely impaired renal function group; and HR, 3.19; 95% CI, 1.42 to 2.72 for the dialysis group compared with those with a normal eGFR. Models run using the maximum troponin concentration in place of the

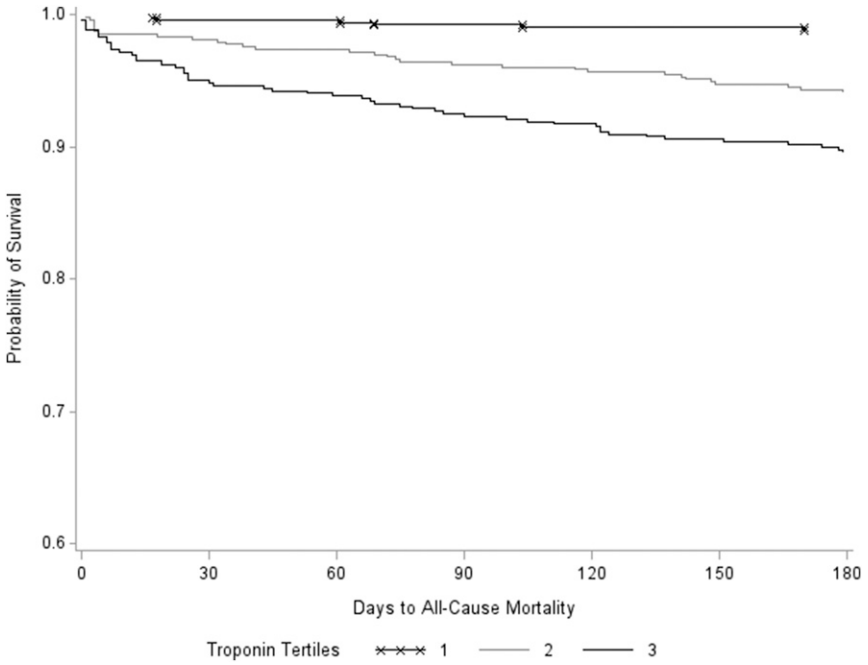

Figure 1. Mortality increased significantly with increasing hs-cTnI by tertile. Kaplan–Meier survival curves for hs-cTnI by tertile.

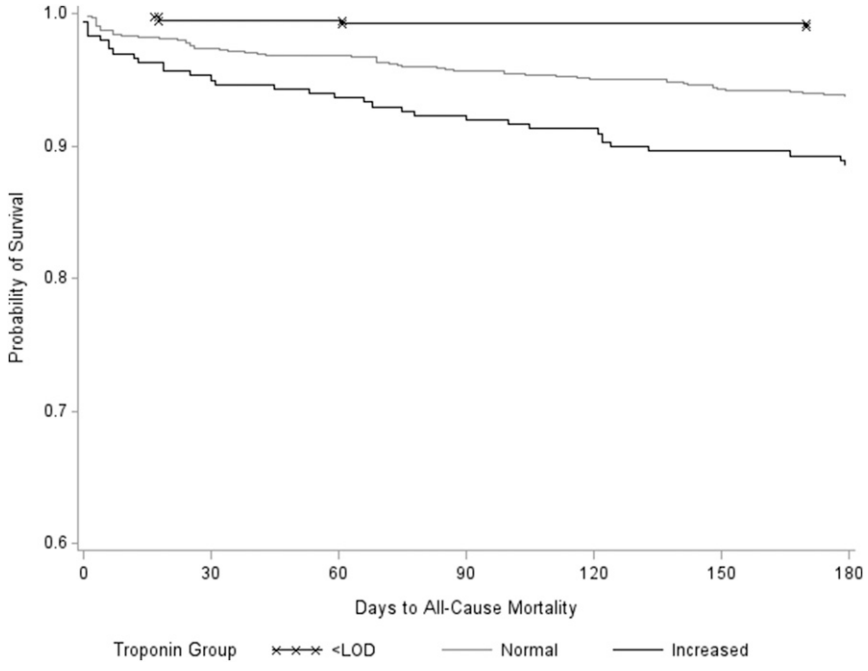

Figure 2. Compared with patients with hs-cTnT concentrations less than LoD, patients with measurable hs-cTnI concentrations between the LoD and the 99th percentile had higher mortality. Kaplan–Meier survival curves by undetectable, normal, and increased hs-cTnI concentrations. ED, emergency department.

baseline values were not meaningfully different and therefore, are not presented. The HR associated with one increase in the troponin tertile was 1.96 (95% CI, 1.41 to 2.72) after adjustment for eGFR status.

DISCUSSION

The implementation and utilization of hs-cTnI and hs-cTnT assays in clinical laboratories are growing globally, except for in the United States, where Food and Drug Administration (FDA) clearance of these assays has lagged.[18,21,22] High-sensitivity assays have been shown to be analytically superior to contemporary and point of care assays, decreasing the rate of false positive and false negative results.[23,24] This has led to the development of strategies for the early rule out and rule in of MI, shortening the time for a diagnostic decision from 6 to 3 hours.[25] Both cTnT and cTnI have been shown to be increased in the absence of acute coronary syndrome,[7] including MI, in patients with renal disease.[5] In patients with ESRD, numerous studies have shown that both cTnI and cTnT are strong prognostic indicators for all-cause mortality, with cTnI showing fewer increases than cTnT but showing a high risk of death.[6,11–13] It is not clear why more than double the number of patients have an increased cTnT versus cTnI in ESRD.[5] Our study on the basis of hs-cTnI both extends and complements these observations, showing both a diagnostic role for MI and prognosis risk assessment in renally impaired patients.

Our study has several important and unique findings. First, we show that, although the hs-cTnI (investigational in the United States) assay provides excellent diagnostic accuracy in patients with symptoms suggestive of MI and higher sensitivity than a contemporary cTnI assay, the clinical specificity and PPV for MI trended downward with decreasing renal function. Second, in contrast, the assay's sensitivity and NPV showed no significant dependence on renal function. These observations support the need to follow serial changes in cTn testing in patients with renal impairment along the universal MI guidelines. Single increased results at any time postadmission may be due to chronic myocardial injury and give a false impression of acute injury or acute MI. Although the European Society of Cardiology has proposed a cutoff concentration for absolute serial change for the Abbott hs-cTnI assay, it is not strongly evidence based, predicated on one non-United States patient population study that addressed type 1 MIs only.[26] In our opinion, it is not valid for

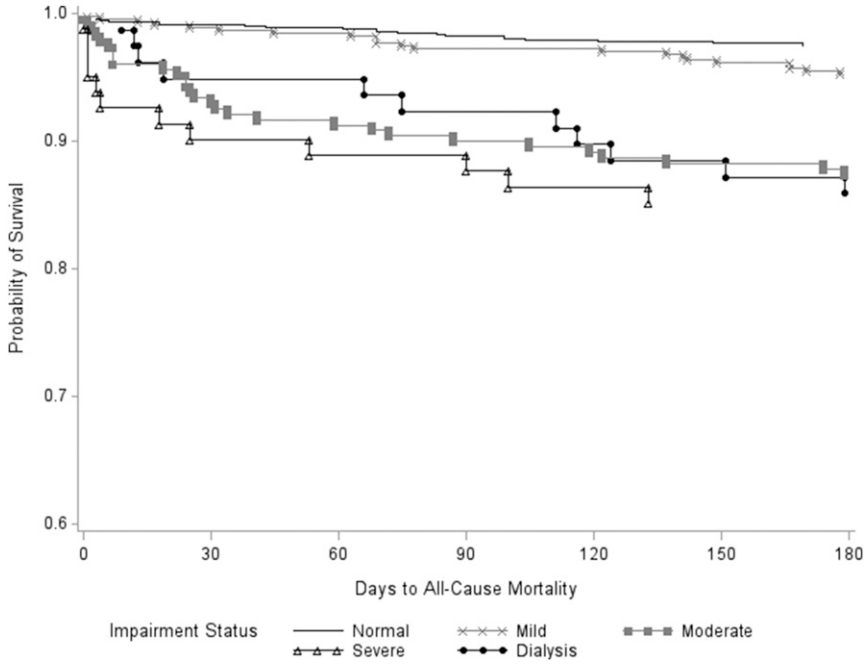

Figure 3. Mortality rates increased with respect to renal impairment independent of hs-cTnI. Kaplan–Meier survival curves with respect to variation in renal function.

our United States study. The PPV for acute MI was lower by a factor of two to three in patients on dialysis than in patients with normal renal function. Third, the role of hs-cTnI as a rule-out test was not significantly affected by renal impairment. Fourth, decreases in renal function and increases in cTnI were both associated with mortality.

Pfortmueller *et al.*[19] observed significantly lower diagnostic accuracy for MI of a single-admission hs-cTnT assay in patients with eGFR<60 ml/min per 1.73 m^2 than in patients with eGFR>60 ml/min per 1.73 m^2. They reported a reduction in the area under the ROC curve at baseline from 0.74 in patients with eGFR>60 ml/min per 1.73 m^2 to 0.54 in patients with eGFR<60 ml/min per 1.73 m^2, a 28% decrease. Our study showed a 36% decrease in the baseline (3 hour; 31% decrease) area under the ROC curve with renal dysfunction for the hs-cTnI from 0.86 (3 hour, 0.93) in patients with eGFR≥90 ml/min per 1.73 m^2 to 0.55 (3 hour, 0.63) in patients on dialysis, both times showing good overall agreement that the diagnostic accuracy of both cTnT and cTnI assays decreased with impaired renal function. Although Twerenbold *et al.*[20] proposed that hs-cTnT and hs-cTnI should use a higher diagnostic cutoff in patients with renal dysfunction to maintain high diagnostic accuracy for MI, our study does not support this conclusion for hs-cTnI. Our study considered multiple subsets of patients with renal dysfunction. We showed that the diagnostic accuracy of the hs-cTnI depended on the magnitude of renal dysfunction as well as dialysis treatment status, suggesting that optimal diagnostic accuracy could not be obtained by using a single higher-cutoff value for patients with eGFR<90 ml/min per 1.73 m^2. Differences between our patient populations may account for this discrepancy between our studies. Twerenbold *et al.*[20] also reported an average eGFR of 49 ml/min per 1.73 m^2 for patients with renal dysfunction, whereas our study patients had a lower average eGFR of 33 ml/min per 1.73 m^2. Furthermore, our study has shown that hs-cTnI specificity and PPV for MI also decreased with impaired renal function in patients not receiving dialysis.

We note several limitations of our study. First, our study findings are on the basis of patients from only one hospital and one hs-cTnI assay (Abbott). We would not expect other manufacturers' hs-cTnI assays to perform differently, but we have come to expect that differences are real between hs-cTnI and hs-cTnT assays. This suggests the need for a direct clinical comparison between hs-cTnI and hs-cTnT assays. Second, the numbers of patients in our groups with severely impaired renal function and on dialysis were low (83 and 77, respectively), possibly reducing the power of our observations in these patients. Third, we did not have enough power to adjust the models beyond the eGFR and cTn categories due to low event rates in the dialysis and severe renal impairment groups. Fourth, a stratified analysis of the prognostic use of hs-cTnI was determined to be insufficiently powered to be undertaken but should be investigated in future studies.

In conclusion, our results suggest that renal dysfunction and dialysis reduced the rule-in performance of hs-cTnI for MI and that all-cause mortality was increased in patients with higher hs-cTnI concentrations at any level of renal dysfunction. However, renal impairment did not exclude the assays' ability to rule out MI. The time is now for clinicians to better understand how high-sensitivity cTn assays will affect their practice, because the assays that are being used globally are coming to the United States.[27]

CONCISE METHODS

After institutional review board approval, we prospectively enrolled consecutive, unselected patients presenting from February 4, 2014 to May 9, 2014 through the emergency department, in whom initial preset serial cTnI measurements (0, 3, 6, and 9 hours) were ordered on clinical indication at Hennepin County Medical Center to rule in/out acute MI (the Use of Troponin in Acute Coronary Syndromes [UTROPIA] Study; NCT02060760). For inclusion, patients needed a baseline cTnI measurement at presentation, at least one additional cTnI within 24 hours of presentation before discharge, and at least one 12-lead electrocardiogram performed. Exclusion criteria were <18 years old, ST-segment elevation MI, pregnancy, trauma, declined to

participate, did not present through the emergency department, or transferred from an outside hospital. For patients with more than one presentation during the study period, we included only the first; 1631 patients without ST elevation MI were enrolled in the UTROPIA Study cohort.[3,4] The Concise Methods sections of refs. 3 and 4 have more detailed information of the primary goals of the UTROPIA Study. For this study, an addition inclusion criteria required an eGFR measurement, which excluded 76 patients, resulting in 1555 study patients.

Fresh EDTA plasma samples were measured with a contemporary cTnI assay (Abbott ARCHITECT $i1000_{SR}$ or $i2000_{SR}$ analyzers; 99th percentile: 0.030 μg/L) and reflexed to an hs-cTnI (investigational) assay (Abbott ARCHITECT $i1000_{SR}$ or $i2000_{SR}$ analyzers). The latter is the same assay used globally outside the United States, but it is not yet FDA cleared for clinical use in the United States. Sex-specific 99th percentile URLs were used for hs-cTnI: women: 16 ng/L; men: 34 ng/L.[2] The hs-cTnI assay's % coefficient of variation was $<$10% at both sex-specific URLs and $<$20% at 2.0 ng/L (LoD).

All patients with at least one hs-cTnI assay result $>$99th percentile were adjudicated according to the Third Universal Definition of MI consensus recommendations by two clinicians after review of all available medical records, including clinical presentation, 12-lead electrocardiogram, echocardiography, angiography, and either the hs-cTnI or contemporary cTnI results. The contemporary assay results used in clinical practice were blinded to the adjudicators. Patients with an adjudication discrepancy were reviewed and adjudicated by a third senior clinician. To guide the adjudication of acute MI in relation to the presence or absence of a significant rise and/or fall of hs-cTnI, an algorithm was developed for the hs-cTnI assay on the basis of biologic variation, with the primary purpose of ensuring that changes within biologic variation were not deemed abnormal. If the initial hs-cTnI value was below the sex-specific 99th percentile, then a rise of $>$69% and/or fall of $>$41% on serial sampling were used to suggest a significant dynamic rise and/or fall.[4] Conversely, if the initial hs-cTnI or contemporary cTnI value was $>$99th percentile, then a change of at least $>$20% was used.[4] eGFR was calculated using the Modification of Diet in Renal Disease equation. Patients were divided into five groups according to their renal function: normal renal function (eGFR$\geq$90 ml/min per 1.73 m^2), mildly impaired renal function (eGFR$\geq$60 to $<$90 ml/min per 1.73 m^2), moderately impaired renal function (eGFR$\geq$30 to $\leq$60 ml/min per 1.73 m^2), severely impaired renal function (eGFR$<$30 ml/min per 1.73 m^2), and on dialysis.

Continuous variables were computed as means ($\pm$SD) and compared with an *F* test. Categorical variables were computed as counts (percentages) and compared with Pearson chi-squared tests. hs-cTnI results were compared with an adjudicated diagnosis to determine the diagnostic accuracy of the hs-cTnI assay. Sensitivity, specificity, PPV, and NPV calculations were determined at each blood draw time (0, 3, 6, and 9 hours) as well as the 95% CIs using binomial proportions. ROC analysis was done at the baseline and 3-hour time points to generate cutoff-specific area under the ROC curve and the associated 95% Wald CI.

Mortality was assessed and compared at 30 and 180 days from admission and plotted on Kaplan–Meier curves. This was done for the five renal function categories as well as tertiles of hs-cTnI at baseline. The prognostic value for hs-cTnI was also examined by eGFR strata. A Cox proportional hazards model also assessed the effect of renal function and baseline troponin on 180-day mortality. All analyses were done using SAS, version 9.4.

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DISCLOSURES

S.W.S. is a consultant for Siemens Healthcare. F.S.A. is on the Board of Directors for HyTest LtD and a consultant for Metanomics Healthcare. I.G., Y.S., A.S., K.S., and C.A.H. declare no conflicts of interest.

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