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1-year mortality following contrast-induced nephropathy

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Abstract: Objective: The aim of this study was to determine the 1-year mortality risk subsequent to Contrast-Induced Nephropathy (CIN) following CECT imaging, relative to other well-recognized predictors of mortality. Methods: We followed a prospective, consecutive cohort of ambulatory patients who received intravenous contrast for CECT for the outcome of death from any cause within 1 year. In a multivariate analysis, we compared CIN with other predictors of mortality: active malignancy, coronary artery disease (CAD), congestive heart failure (CHF) and age ≥70 years. Anticipating that terminal cancers would account for the majority of deaths in this population, we also analyzed the subset of patients without an active malignancy at the time of enrollment. Results: We followed 633 patients and 46 died (7%, 95%CI: 5-9%) within 1 year. The incidence of CIN was 11% (95%CI: 8-14%). Active malignancy (HR 9.2, 95%CI: 5.1-16.8), CIN (HR 2.4, 95%CI: 1.3-4.6), CHF (HR 2.1, 95%CI: 1.0-4.2), CAD (HR 2.2, 95%CI: 1.0-5.5) and age ≥70 years (HR 1.8, 95%CI: 1.0-3.8) were significant predictors of all-cause mortality. Among patients without active malignancies, the mortality rate was 4% (25/580, 95%CI: 3-6%) and CIN (HR 4.0, 95%CI: 1.7-9.6) and age ≥70 years (HR 3.7, 95%CI: 1.4-9.7) were significantly associated with death, whereas CAD (HR 2.5, 95%CI: 0.8-7.7) and CHF (HR 1.8, 95%CI: 0.6-5.3) were not. Conclusions: The development of CIN following CECT is associated with an increased likelihood of death at 1 year among patients with and without active malignancies, comparable to CAD, CHF and advanced age.

Keywords: Acute Kidney Injury, Mortality, Contrast Media, Computed Tomography, Outpatients

1. Introduction

Expert guidelines define contrast induced nephropathy (CIN) as a 25% relative increase or 0.5mg/dL absolute increase in serum creatinine value, measured 2-7 days after exposure to iodinated contrast.[1, 2] The clinical significance of CIN remains controversial, especially in the setting of intravenous contrast after contrast enhanced computed tomography (CECT).[3, 4] Most outcome studies of CIN have been conducted in patients exposed to intra-arterial contrast coronary angiography.[1, 5] Despite an exponential increase in persons receiving intravenous iodinated contrast material for CECT in United States,[6] to the best of our knowledge, no study has reported long-term outcomes in the population undergoing CECT.

We have recently published data from a prospective, cohort study of over 600 patients who received intravenous contrast for CECT for a range of indications in the outpatient setting. Patients were followed for the development of CIN and for short-term outcomes (45-days following contrast exposure) including severe renal failure and death from renal failure.[7] Notably, this was a heterogeneous population with a low overall risk for CIN and severe outcomes; only 10% of this population had preexisting renal insufficiency (estimated glomerular filtration rate [eGFR] <60ml/min/1.73m^2)[8] and 51% were discharged directly to the outpatient setting following evaluation CECT. We found that CIN occurred in 11% of patients and was associated with a marked increased risk of severe renal failure and death from renal failure at 45-days (relative risk 48, 95% CI: 8 to 302).[7] The objectives of the present study were to measure the outcomes of CIN and subsequent 1-year mortality, and to test if CIN was an independent predictor of 1-year mortality in this cohort, after adjusting for other well-recognized predictors of mortality.

2. Methods

2.1. Study design

This was a prospective, observational cohort study, conducted at a single-center aimed at documenting the incidence of CIN and death at 1-year. This study was approved by the institutional review board and written informed consent was obtained from study participants.

2.2. Study Setting

Patients were enrolled from the emergency department (ED) of Carolinas Medical Center in Charlotte, NC: an urban, academic center with over 900 beds and the ED staffed by board-certified emergency medicine physicians 24/7. Over 110,000 patients are treated in this ED annually. CECT imaging studies were performed on 2 Multi-Detector Siemens Somatom Sensation 64-slice scanners (Siemens Medical Solutions USA, Inc, Malvern, PA) and interpreted, in real-time, by on-site, board certified radiologists. All patients received Iopamidol-370 (Isovue-370®, Bracco Diagnostics, Princeton, NJ). The institution also utilizes a centralized medical record system for 25 hospitals and over 100 primary and specialty practice locations, allowing the follow-up of a large, ambulatory population for outcomes, with reasonable reliability.[7, 9]

2.3. Selection of Participants

The methods of enrollment have been previously described.[7, 9] Briefly, we enrolled consecutive patients undergoing CECT. Exclusion criteria included: 1) age <18 years, 2) hemodialysis or peritoneal dialysis within 45 days prior to enrollment or documented prior physician-directed plans to start dialysis within 45-days after enrollment, 3) kidney transplant prior to or planned at the time of enrollment, 4) intravenous contrast for any reason within 14 days prior to enrollment, 5) pregnancy or post-partum <48 hours, 6) patients with immediately life threatening injuries as classified by the institutional guidelines, 7) the inability to provide written, informed consent, or 8) patient-stated unavailability for the follow-up blood draw. Patients that were enrolled, but did not receive contrast (e.g., the study was canceled or changed to a non-contrasted study after the patient was enrolled) were also excluded.

2.4. Study Protocol

The methods of data collection have been published previously.[7] Briefly, patients were enrolled at the time an order was placed by the ED provider for a CECT of any body-region (Centricity®, GE Healthcare, Chalfont St. Giles, UK). Data included the presence or absence of risk factors for 1-year mortality at the bedside, in real-time through a combination of patient interview, review of the ED chart and provider interview. Using standard phlebotomy techniques, we collected blood at the time of enrollment and at least 48 hours but not more than 169 hours (2 to 7 days) following contrast administration for serum creatinine measurements (i-STAT, Abbott Point of Care, Inc; East Windsor, NJ).

2.5. Outcome Determination

The primary outcome of this study was defined as death from any cause within 1-year of the enrollment CECT. We used a rigorous, sequential, and redundant approach, executed in the following order: 1) A telephone interview with the patient or next of kin, 2) An explicit search of the medical record for evidence of death, and 3) A search of the Social Security Death Index (SSDI).[7, 9] For telephone follow-up, failure was declared after five 5 separate attempts made at different times on different days of the week over a two week period. We also reviewed the electronic medical record for all participants, starting at 2-years post-enrollment, to serve as a confirmatory (in the event of telephone success) or primary method (in event of telephone failure). Finally, we conducted a search of the social security death index for patients whose status could not be determined by either telephone interview or electronic medical record review. Discrepancies were resolved using a blinded adjudication process requiring the consensus of 2 out of 3 independent evaluators.[7]

2.6. Data Analysis

With the 1-year mortality rate as the dependent variable, we used a Cox regression multivariate survival analysis to determine the hazard ratios (HRs) for the independent variables of 1) CIN; 2) Age ≥70 years at the time of enrollment; 3) coronary artery disease (CAD), determined by patient report of a prior myocardial infarction or physician-determined narrowing of the coronary arteries requiring medical or surgical intervention; 4) congestive heart failure (CHF) ,defined by a patient report of a physician-determined diagnosis requiring therapy and the presence of CHF recorded by the provider in the medial chart at the time of enrollment; and 5) active malignancy, defined as the presence of a malignancy with ongoing or planned physician-directed chemotherapy, radiation, and/or surgical treatment as reported by the patient or recorded in the medical chart at the time of enrollment. Conditions identified subsequent to the index visit were not considered a part of the study-definition for independent variables. For example, patients with a malignancy diagnosed after the index visit were classified as cancer-free in our analysis. Anticipating that deaths attributable to terminal cancers would account for the majority of deaths observed within a population undergoing CECT imaging studies, we also performed a separate analysis of the subset of patients without a history of active malignancy at the time of study enrollment.

Finally, the baseline serum creatinine measurement and patient characteristics were also used to determine the prevalence of baseline renal insufficiency defined as an eGFR <60 mL/min/1.73m^2 calculated using the Modification in Diet in Renal Disease (MDRD) equation.[8] We report overall outcome incidence, population characteristics and presumptive risk factors as proportions with associated 95% confidence intervals (95%CI) calculated using the Clopper-Pearson method. We

performed all statistical analyses using STATSDirect V3.3 software (Chesire, UK).

3. Results

We followed 633 patients that received intravenous contrast for CECT in the ED, of which, 53/633 (8%, 95%CI 6 to 11%) had an active malignancy identified at enrollment. Patient enrollment and outcomes are summarized in Fig. 1 and population characteristics, including the prevalence of mortality risk-factors and literature-defined risk-factors for CIN at enrollment, are summarized in Table 1. Notably, only 10% of patients enrolled in this study had measurable baseline renal insufficiency, 17% had diabetes mellitus and approximately one-half were discharged from the emergency department following the CECT. The majority of CECT studies (571/633, 90% 95%CI 88 to 92%) were obtained for non-traumatic indications and imaging of the abdomen and/or pelvis accounted for over half of the CECT studies conducted (54%, 95%CI 50 to 58%) and174/633 (27%, 24 to 31%) were pulmonary angiography studies.[7, 10]

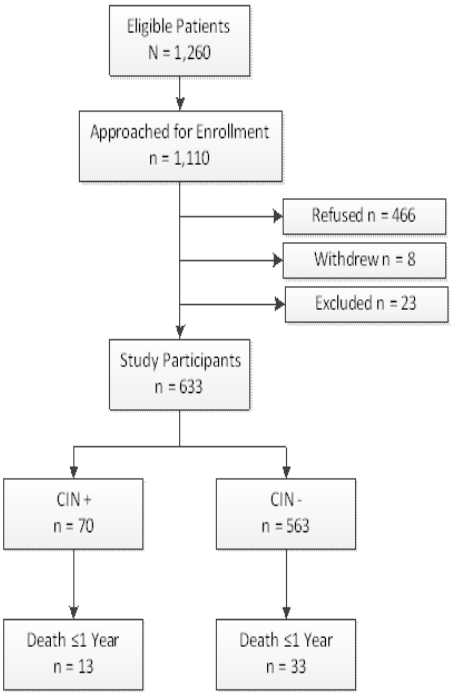


Figure 1. *Enrollment and selection of participants.*

The follow-up blood draw allowed the determination of CIN (presence or absence) in 431/633 patients (68%, 95%CI: 64 to 72%), including 250 patients who were not inpatients at the time of follow-up. The majority of enrolled patients (603/633, 95%, 95%CI: 93 to 97%) reported that their primary access to follow-up care was within the CHS system and survival or death was definitively determined by a combination of telephone interview and medical record review for 553 patients (87%, 95%CI 85-90%). There were no discrepancies in the reporting of a death event from telephone interview and medical record review. Query of the SSDI identified 4 deaths, not previously identified by telephone interview and medical record review.

Table 1. *Clinical characteristics of study participants at enrollment.*

Enrollment Characteristics	**Unselected Cohort N = 633**	**Subset Without Malignancy N = 58**
Female Gender, % (95%CI)	57 (53 to 61)	56 (52 to 60)
Caucasian, % (95%CI)	40 (36 to 44)	39 (35 to 43)
African American, % (95%CI)	52 (48 to 56)	52 (48 to 56)
Other/Unknown Race, % (95%CI)	8 (6 to 11)	8 (6 to 11)
Age ≥ 70 years, % (95%CI)	7 (5 to 10)	7 (5 to 10)
Active Malignancy, % (95%CI)	8 (6 to 11)	N/A
Congestive Heart Failure, % (95%CI)	5 (3 to 7)	6 (4 to 8)
Coronary Artery Disease, %](95%CI)	7 (5 to 10)	5 (3 to 7)
Hypertension, % (95%CI)	44 (40 to 48)	43 (38 to 47)
Diabetes Mellitus, % (95%CI)	17 (15 to 21)	17 (14 to 21)
Renal Insufficiency*, % (95%CI)	10 (6 to 10)	9 (7 to 12)

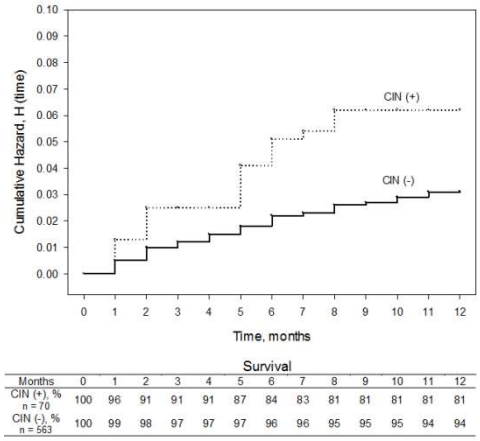
95%CI = 95% confidence interval.

**Estimated glomerular filtration rate <60 mL/min/1.73m^2.*

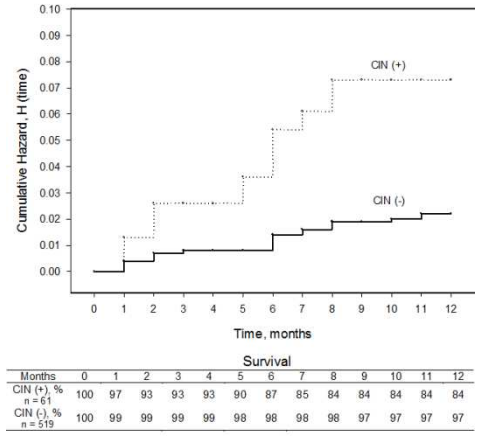
The outcome of CIN within one week was observed in 70/633 patients (11%, 95%CI: 9 to 14%) and the outcome of mortality at one year was observed in 46/633 (7%, 95%CI 5 to 9%) The one-year mortality rate after CIN was 13/70 (18%) compared with 33/563 (6%) who did not develop CIN (risk ratio = 3.1, 95% CI 1.7 to 5.4). The multivariate Cox regression analysis revealed age ≥70 years (HR 1.8, 95%CI: 1.0-3.8), CAD (HR 2.2, 95%CI: 1.0-5.5), CHF (HR 2.1, 95%CI: 1.0-4.2), active malignancy (HR 9.2, 95%CI: 5.1-16.8), and CIN (HR 2.4, 95%CI: 1.3-4.6) all as significant predictors of all-cause mortality (likelihood ration X2 = 59.9 df = 5 p<0.0001). Approximately one-half of patients (21/46, 46%, 95% 31 to 61%) who died within 1-year of enrollment had active malignancy at enrollment. The all-cause mortality rate among cancer-free patients was 4% (25/580, 95%CI: 3-6%). In this subset, the incidence of CIN remained unchanged: 11% (95% CI: 8 to 13%). Within this subset of cancer-free patients, CIN (HR 4.0, 95%CI: 1.7-9.6) and age ≥70 years (HR 3.7, 95%CI: 1.4-9.7) were

significantly associated with death at 1-year, whereas CAD (HR 2.5, 95%CI: 0.8-7.7) and CHF (HR 1.8, 95%CI: 0.6-5.3) were not (X2 = 18.2 df = 4 p = 0.0011).

The adjusted cumulative hazard curves and proportional survival for mortality at one year, between CIN+ and CIN- patients for the unselected cohort and malignancy-free subset are shown in Figures 2a and 2b.



(a)



(b)

Figure 2. *a Adjusted cumulative hazard for 1-year mortality in the unselected cohort. CIN 11% (95%CI: 8 to 14%); 1-yr Mortality 7% (95% CI: 5 to 9%); Likelihood Ratio X2 = 59.9 df = 5 p<0.0001. b Adjusted cumulative hazard for 1-year mortality in the subset of patients without active malignancies at enrollment. CIN 11% (95%CI: 8 to 13%); 1-yr Mortality 4% (95% CI: 3 to 6%); Likelihood Ratio X2 = 18.2 df = 4 p = 0.0011.*

4. Discussion

In this prospective cohort of patients who were exposed to intravenous iodinated contrast for the purpose of CT imaging, CIN was a significant, independent risk factor for long-term mortality. The multivariate model found that CIN was comparable to advanced age or prior heart disease as a prognosticator for death within one year, and CIN remained a significant predictor of mortality even among patients without active malignancies. This increased risk of death after CIN was observed within a patients sample that might be considered low risk for acute kidney injury inasmuch as one-half of the cohort was discharged from the emergency department after the CECT scan, only 10% of patients had baseline renal insufficiency, and only 17% of patients had diabetes mellitus. In fact, we did not observe a significant difference in the incidence of CIN between patients hospitalized at enrollment (10%, 95%CI 7 to 13%) compared to those discharged directly from the emergency care setting (13%, 95%CI 9 to 17%). Strengths of this study include the patient sample, which was derived from a large, heterogeneous population enrolled prior to the following: 1) availability of outcomes results of the CECT; 2) all related treatment initiation; 3) the disposition decision from the emergency department (admission or discharge); and, of course, 4) the primary outcomes of CIN or death. We submit that that we executed a rigorous and demanding protocol to obtain the follow-up blood draw and mortality endpoints.[11] We were able to definitively determine 1-year survival through telephone follow-up and/or definitive medical record review for 87% of our population, and query of the SSDI for the other 13%.

These data provide a new perspective to existing literature as the first to demonstrate in the outpatient CECT population that 1) CIN is significantly associated with a severe outcome (death), observed over a long-term follow-up period, and that 2) CIN remained a significant predictor even after adjustment for age, prior heart disease (coronary artery disease or CHF), or malignancy. The pathophysiology of CIN and the confounding effects of comorbidities have limited the ability to define a causative relationship between contrast exposure and outcomes of acute kidney injury (AKI) or death in the present and prior studies.[5, 12] Our data reinforce the notion that CIN has an indolent course that could easily go unrecognized, particularly in the ambulatory and emergency care settings, because of an absence of a protocol explicitly designed to compulsorily measure a repeat blood sample within the 2 to 7 day follow-up period. Even with a blood sample in hand, clinicians lack a validated biological marker that directly indicates the presence of AKI from CIN. Instead, we must rely on serum creatinine, an indirect marker of glomerular filtration rate that has many well-known limitations as a biomarker for AKI.[13] Despite the inadequacies of creatinine, prior data demonstrates that AKI, from any cause, significantly contributes to long-term mortality and morbidity and our study is consistent with these data.[14-16]

Ideally, the causative role of CIN would be established in a well-matched, unexposed control group. However, in real clinical practice, the indications for CECT inherently define a fundamentally different patient sample than would be obtained either from a population undergoing CT imaging without iodinated contrast, or not undergoing CT imaging at all. It would be ethically implausible to define a direct control group by experimentally withholding contrast for a CECT scan ordered as part of standard medical care. However, Solomon et al were able to compare the incidence of CIN and subsequent mortality in patients

enrolled in randomized of a trial designed to study the differential risk of CIN from low-osmolar versus iso-osmolar contrast. In this study, a lower incidence of CIN was also associated with a significantly lower incidence of subsequent mortality at 1 –year. This study was limited to patients with multiple risk-factors for CIN including moderate to severe renal insufficiency, limiting a direct comparison to the unselected ambulatory population.[12] Similarly, the literature is replete with studies that demonstrate that an interval increase in serum creatinine following iodinated contrast exposure is strongly associated with subsequent development of severe renal failure and increased risk of mortality.[5] While the current state of the literature does not directly establish the causal role of CIN, our observed risk ratio for mortality of 3.1 is comparable to that observed with AKI from heterogeneous causes.[16]

This study has several limitations. First, we enrolled patients only from a single, albeit, large academic center. Our study also excluded critically ill and injured patients, which accounted for approximately 20% of the overall ED patient population. As such, the results may not be generalizable to other populations. Second, this study required both an enrollment and follow-up blood draw and short- and long-term follow-up, which likely accounts for the 40% rate of at which eligible emergency department patients declined to participate. Similarly, 32% of patients did not complete the follow-up blood draw. However, approximately half of patients were discharged from the emergency department on the day of enrollment and another 22% of patients were discharged to the outpatient setting within 48 hours of contrast exposure. Finally, it is possible that the timing of the follow-up blood draw may not have captured the peak-creatinine level in some patients. The standard definition for CIN typically cites an interval serum creatinine level measured 48 to 72 hours after contrast exposure and 71% of our follow-up samples were obtained in this time frame.[7] However, current literature estimates that this restriction may miss up to 60% of CIN cases.[2, 17-21] Taken together, the overall effect of these limitations has likely resulted in an underestimation of both the incidence of CIN and resulting risk-association with mortality at one year. Thus, our results represent a conservative estimate of the association of CIN with long-term mortality, which is likely to be greater than what we report in this study.

In conclusion, the development of CIN following CECT in the ambulatory setting is associated with an increased risk of subsequent mortality over the following year, after adjusting for other well-recognized risk factors for mortality, including age $\geq$ 70 years, active malignancy, CAD and CHF. Among patients without active malignancies at the time of CECT, CIN and age $\geq$ 70 years remained significantly associated with 1-year mortality. These data implicate the need to test outcomes-based imaging protocols that limit exposure to intravenous iodinated contrast in the ambulatory and emergency care settings.

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