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Contrast-Induced Nephropathy (CIN) and Renal Replacement Therapy (RRT) after CIN, after IV dye in the Emergency Department in Geriatric Patients: Predicting If Renal Replacement Therapy Occurs After The Emergency Room: *The Geri PIRATE Study and Baird Hypothesis*

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ABSTRACT

Iodinated radio contrast agent–induced nephropathy (CIN) is a known complication of radiologic or angiographic procedures. Contrast-induced nephropathy (CIN) is an impairment of renal function, defined as either a 25% increase in serum creatinine (SCr) from baseline or 0.5 mg/dL (44 µmol/L) increase in absolute value, within 48-72 hours after intravenous contrast administration.

The primary objective of this study was to attempt to further define and identify the elderly patient population at risk for CIN after computerized tomography studies utilizing intravenous radio contrast media. A secondary objective was to attempt to define and predict which patients developing CIN will require RRT.

Contrast-induced nephropathy, by definition, is a self-limiting disease. However, there is still great concern by ED physicians concerning causing CIN in their elderly patients. Fear of causing damage to the kidneys could lead to doing less accurate diagnostic tests and inferior and less safe workups. The data show that the incidence of CIN in the geriatric population studied requiring dialysis was 0%. Risk factors did not play a major role in causing a larger change from baseline creatinine. Risk factors did not play a major role in causing a larger percent change from baseline creatinine. Lastly, the geriatric kidney might have a counter-intuitive protective effect from IV contrast for an as yet unknown reason. It appears, according to our study, that the older the kidney, the better that kidney tolerates IV contrast. Two of the authors of this study, (JE, VS) have referred to this hypothesis as the "Baird Hypothesis."

KEYWORDS

Contrast Induced Nephropathy (CIN); Contrast induced nephropathy (CIN) and Geriatric Patients; Contrast Induced Nephropathy (CIN) in Emergency Medicine.

INTRODUCTION

Iodinated radio contrast agent–induced nephropathy (CIN) is a known complication of radiologic or angiographic procedures. Contrast-induced nephropathy (CIN) is defined as the impairment of renal function. It is measured as either a 25% increase in serum creatinine (SCr) from baseline or 0.5 mg/dL

(44 µmol/L) increase in absolute value, within 48-72 hours after intravenous contrast administration. Several mechanisms have been proposed to explain the pathogenesis of CIN. Measures aimed to prevent CIN are based on these pathogenic mechanisms. Renal ischemia is currently considered the primary mechanism for CIN. It is well known that the outer renal medulla has an extremely low oxygen tension (PO2 10–20 mm Hg), as the result of countercurrent oxygen exchange and removal between the vasa rectae and utilization of oxygen by active tubular transport by the ascending loop of Henle. Administration of contrast media has been shown to selectively further reduce oxygen tension in this area of the kidney by a duel mechanism. The first is reduction in renal blood flow, mediated by release of vasoconstrictive compounds such as endothelin and adenosine, an effect that is magnified by blockade of vasodilatory compounds such as nitric oxide and prostaglandins. The second is increased oxygen utilization caused by increased work of active transport in response to an osmotic diuresis induced by contrast media in the renal tubule [4].

The risk of radio contrast agent–induced acute tubular necrosis (ATN) can be reduced by identification of risk factors in patients for who contrast studies are being considered [2]. The most important risk factors for radio contrast agent–induced ATN include preexisting renal insufficiency, diabetes mellitus, multiple myeloma, age greater than 60 years, volume depletion, and higher doses of contrast material [1]. Among these, preexisting renal insufficiency is the most important. Advanced age also appears to make ATN more likely. Before contrast medium is administered to a high-risk patient, it should be established that there is a compelling reason to perform the contrast study and that there is no adequate alternative to using a contrast agent [2].

The incidence of CIN, which by definition, is a self-limiting disease, varies from 3% to 7% in patients without any risk factors, but can be as high as 50% in patients with moderate to advanced chronic kidney disease [1]. Despite the use of newer contrast media and the implementation of preventive measures, only a small fraction of these patients require renal replacement therapy (RRT) [3].

The literature is replete with many studies that propose strategies to prevent or decrease the incidence of CIN. Many of these studies involve therapies administered to patient's prior to and after a contrast study to prevent CIN's occurrence. Most of these strategies have not demonstrated proven benefit.

It is not clear which patient characteristics are associated with CIN leading to the need for RRT.

The primary objective of this study was to attempt to further define and identify the elderly patient population at risk for CIN after computerized tomography studies utilizing intravenous radio contrast media. A secondary objective was to attempt to define and predict which patients developing CIN will require RRT

MATERIALS AND METHODS

Research Design and Methods

The study was retrospective in design. The population was patients 70 years of age and older who received an IV contrast load in the emergency department in the years 2007-2012. The emergency departments selected were three community teaching emergency departments.

Patients > 70 years of age that received a discharge diagnosis of CIN were reviewed. Of these charts, patients who received the IV contrast load within the emergency department system prior to the diagnosis of CIN were studied. Risk factors for CIN, based on historical data discussed above in the background statement, were assessed with each patient. The serum creatinine and estimated glomerular filtration rates based on the KHS laboratory prior to contrast load, were used.

The primary objective of this study was to attempt to further define and identify the elderly patient population at risk for CIN after computerized tomography studies utilizing intravenous radio contrast media. A secondary objective was to attempt to define and predict which patients developing CIN will require RRT. CIN was defined as a 25% increase in serum creatinine (SCr) from baseline or 0.5 mg/dL (44 µmol/L) increase in absolute value, within 48-72 hours of intravenous contrast administration.

The data collected included

- Patient Age
- Patient Gender
- Patient Race
- Patient Weight
- Type of ED Contrast Study
- ED creatinine
- CIN (highest) creatinine
- Admitting diagnosis
- Final diagnosis
- CIN patients who required RRT
- Pre-existing CKD
- Pre-CIN hemodialysis [prevalence, pre-CIN]

- Post-CIN hemodialysis [incidence, post-contrast]
- Risk factor: CAD
- Risk factor: Diabetes mellitus
- Risk factor: Multiple myeloma
- Risk factor: ACE Inhibitor
- Risk factor: Proteinuria
- Risk factor: Gout
- Risk factor: CHF
- Risk factor: history renal surgery [e.g. nephrectomy, neph rostomy tube in place]
- MDRD: Estimated GFR (eGFR) using Modification of Diet in Renal Disease (MDRD) formula
- Estimated creatinine clearance rate using Cockcroft-Gault formula
- Increase in Creatinine: Baseline in ED vs CIN maximum level
- Percent increase in Creatinine: Baseline in ED vs CIN maximum level

RESULTS

Participant Demographic Data

There were 31 participants in the study. The mean age was 78.16 years of age. [StDev 6.16] The youngest patient was 70 years of age and the oldest patient was 96 years of age. The median age was 76. 23 of the respondents were female (74%) and 8 of the respondents were male (26%) The two distributions (percent patients by gender) were statistically different, based on the p-value for difference in proportions. (p = < 0.05)

10 participants were African-American (32%). 21 participants were White (68%) The two distributions were not statistically different, based on the p-value for difference in proportions. (p = 0.07) The mean weight of participants was 84.96 kg. [StDev 26.10] The lowest weight was 45.4 kg and the highest weight was 137.9 kg. The median weight was 81 kg. The mean weight for African-American participants was 94.68 kg, with a median weight of 87.15 kg. The mean weight for white participants was 80.33 kg with a median weight of 80.5 kg. The differences in weight by race were not statistically significant. (Two sample T-test, p = .186) The mean weight for female participants was 85.04 kg, with a median weight of 81.2 kg. The mean weight for male participants was 84.71 kg with a median weight of 84.75 kg. The differences in weight by gender were not statistically significant. (Two sample T-test, p = .972).

Type of ED Contrast Study

CTA of the chest (35.5%) and CT abdomen and pelvis (35.5%) were the two largest categories. Together, they comprised 70% of the studies ordered.

ED Serum Creatinine: The mean initial (baseline ED, pre-contrast) creatinine was 1.0 [StDev .28]. The minimum creatinine was 0.42. The maximum was 1.6. (Figure 1).

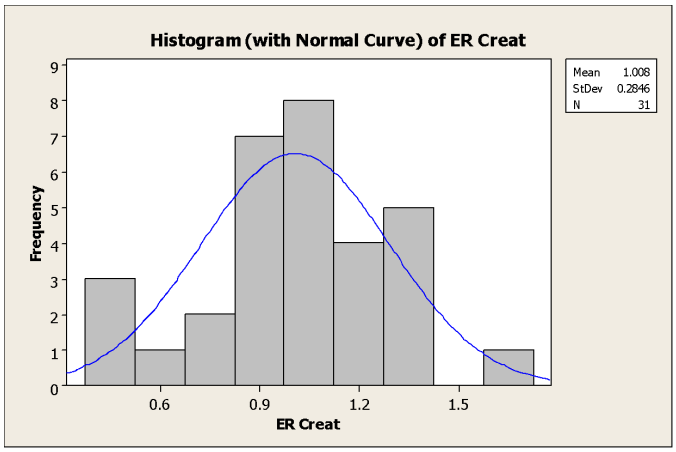

Figure 1: Histogram of baseline ED creatinine data.

ED Serum Creatinine by Gender: The mean ED creatinine for female participants was 0.96. The mean ED creatinine for males was 1.14. ED creatinine by gender was not statistically significant. (p = .08). **CIN (highest) Creatinine:** The highest value creatinine measurements showed a mean of 2.21. The minimum was 1.15. The maximum was 5.5. The median value was 1.9. **Final Diagnosis:** The 31 cases comprised 26 discrete diagnoses.

The most common were:

- COPD Exacerbation: 3 cases 9.68%
- Pneumonia 3 cases 9.68%
- Small bowel obstruction 2 cases 6.45%

The remaining 23 diagnoses had only a single case. **CIN patients who required RRT:** No patients (0%) required RRT.

Pre-CIN hemodialysis: None of the patients had a history of pre-CIN dialysis

Post-CIN hemodialysis: None of the patients underwent of dialysis after the CIN episode, during the time of hospitalization.

Pre-existing CKD (Chronic Kidney Disease): 6 patients (19.4%) had a history of CKD. The remaining 25 patients (80.6%) did not.

Stage of Pre-existing CKD: Of the six patients with pre-existing CKD, 3 had Stage 2 disease (9.7% of total patients) and 3 had Stage 3 disease (9.7% of total patients). As noted above, the

remaining patients had no history of CKD (80.6%).

Risk factors: The CIN cohort in this studied was analyzed in reference to risk factors determined from a review of the literature. 9 factors are reviewed in Table 9. There were no cases of multiple myeloma or previous renal surgery.

Table 1: Pre-Existing Risk Factors for CIN.

Pre-Existing Risk Factor for CIN (From Literature Review)	Count	Present (%)	Count	Absent (%)	P value
Proteinuria	18	58.10%	13	41.90%	p = 0.20
DM	14	45.20%	17	54.80%	p = 0.44
ACE inhibitor	9	29%	22	71.00%	p = < .01
Pre-existing CKD	6	19.40%	25	80.60%	p = < .001
CAD	6	19.40%	25	80.60%	p = < .001
Gout	4	12.90%	27	87.10%	p = < .001
CHF	4	12.90%	27	87.10%	p = < .001
Multiple myeloma	0	0%	31	100.00%	NA
Renal surgery	0	0%	31	100.00%	NA

Pretreatment: 21 patients (67.7%) received pretreatment. 10 patients (32.3%) received no pretreatment. These two groups are different statistically. (p = .003) The types of pretreatment were varied. The most common pre-treatment was none (10 patients, 32.2%) When pre-treatment was given, the most common was NS 1 liter (10 patients, 32.2%). Mucomyst (600 mg po) was given in one patient (3.2%). (Table 3, 4).

Table 2: Types of Pretreatment.

Pretreatment_1	Count	Percent
Mucomyst 600	1	3.23
none	10	32.26
NS X 1L	10	32.26
NS X 2L	2	6.45
NS X 3L	3	9.68
NS X 500 cc	5	16.13
N =	31	

MDRD Data: The mean MDRD result was 54.03. (StDev 8.08) The minimum was 36. The maximum was 60.

C-G data: (Estimated creatinine clearance rate (eC_{Cr}) using Cockcroft-Gault formula: The mean estimated creatinine clearance rate with the Cockcroft-Gault (C-G) formula was 61.05. (StDev 23.82).

Increase in Creatinine: Baseline in ED vs CIN maximum level: The mean increase in creatinine from the baseline ED measurement to the maximum CIN level creatinine was 1.205 (StDev 0.813). The median increase was 0.96 (Figure 2).

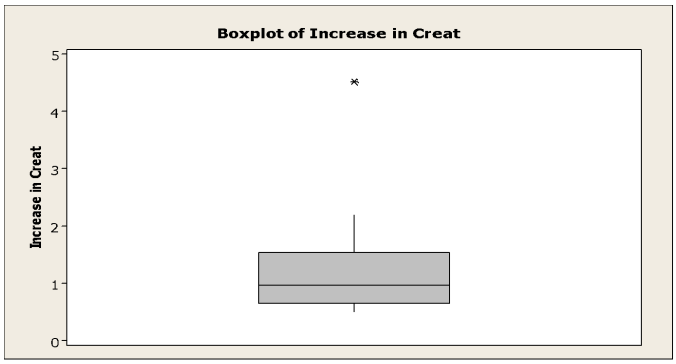

Figure 2: Boxplot: Increase, Baseline in ED to CIN maximum level.

Percent increase in Creatinine: Baseline in ED vs CIN maximum level: The mean percent increase in creatinine from the baseline ED measurement to the maximum CIN level creatinine was 130% (StDev 105.5%). The minimum increase was 35.7%. The maximum increase was 461%. The median increase was 100%. The 75th percentile (Q3) for percent increase was 147.7 % (Figure 3).

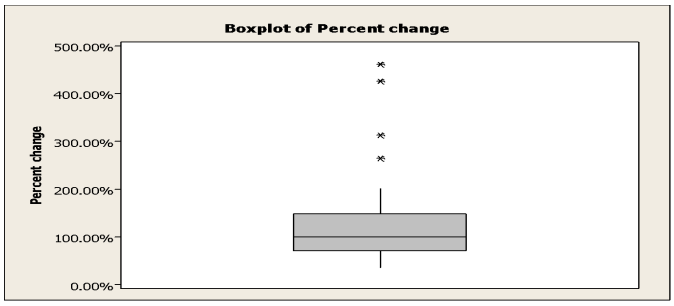

Figure 3: Boxplot display, percent change in creatinine.

Correlation Analysis

A summary of various correlations is found in Table 3. The MDRD and C-G did not statistically correlate. The MDRD showed good correlation with the ED creatinine, in the direction of a lower MDRD tracking with a higher ED creatinine (negative correlation). This was highly statistically significant. Pearson correlation of MDRD and ED Creat = -0.738 (P-Value = 0.001) The C-G also correlated with the ED creatinine, but more weakly than the MDRD. The correlation was also negative (lower C-G tracking with a higher ED creatinine. Neither the MDRD nor the C-G showed statistically significant correlation with the CIN creatinine. The MDRD was superior in its correlation (Table 3).

Neither the MDRD nor the C-G showed good correlation with the absolute increase (delta) between the ED creatinine and the CIN creatinine (Table 3).

Neither the MDRD nor the C-G showed good correlation with the percent increase between the ED creatinine and the CIN

creatinine. The Pearson correlation of C-G and percent change was better than the MDRD (0.404). The p-value for this correlation was statistically significant. (P-Value = 0.02) (Table 3).

Table 3: Correlation Results: MDRD and C-G related.

Correlation Results: MDRD and C-G related	Pearson correlation	p-value
Correlations: MDRD, C-G with each other	0.269	0.14
Correlation: MDRD v C-G with ED Creatinine		
Correlations: MDRD, ER Creat	-0.738	0.001
Correlations: C-G, ER Creat	-0.352	0.05
Correlation: MDRD v C-G with CIN Creatinine		
Correlations: MDRD, CIN Creat	-0.162	0.39
Correlations: C-G, CIN Creat	0.137	0.46
Correlation: MDRD and C-G v. Absolute Increase in Creatinine		
Correlations: MDRD, Increase in Creatinine	0.087	0.64
Correlations: C-G, Increase in Creatinine	0.269	0.14
Correlation: MDRD and C-G and Percent Change		
Correlations: MDRD, Percent change	0.299	0.10
Correlations: C-G, Percent change	0.400	0.02

Relationship of Age Group [70 to 84, ≥ 85] to core creatinine metrics: Patients ≥ 85 years of age group showed a statistically higher baseline creatinine level (p = 0.03) The CIN creatinine was also higher in the older age group, but this difference was not statistically significant. (p = 0.68) The delta creatinine (baseline vs CIN level) was higher in the 70 to 85 years of age group. This difference was not statistically significant. (p = 0.47).

Relationship of Risk Factors to ED Baseline Creatinine: 13 factors were studied in relationship to the baseline creatinine. The results are shown in Table 4.

Table 4: Risk Factors and ED Baseline Creatinine.

	Risk Factor and ER Baseline Creatinine				
	Factor Present		Factor Not Present		
Pre-Existing Possible Risk Factor for CIN	**Average**	**StDev**	**Average**	**StDev**	**p-value**
Proteinuria	1.04	0.30	0.97	0.27	0.35
DM	1.02	0.29	1.00	0.29	0.82
ACE inhibitor	1.04	0.28	0.99	0.29	0.68
CAD	0.99	0.13	1.01	0.31	0.83
Gout	1.04	0.31	1.03	0.28	0.82
CHF	1.03	0.27	1.01	0.27	0.89
Multiple myeloma	n/a	n/a	n/a	n/a	n/a
Renal surgery	n/a	n/a	n/a	n/a	n/a
Race: African-American	1.14	0.24			
Race: Caucasian			0.95	0.29	0.07
CKD	1.24	0.29	0.95	0.26	0.06
HD (pre-existing)	n/a	n/a	n/a	n/a	n/a
Gender: Female	0.96	0.30			
Gender: Male			1.14	0.20	0.09
Pre-treatment regimen					
Fluids and/or mucomyst no/yes	1.01	0.27	1.00	0.30	0.94

Relationship of Risk Factors to CIN Creatinine: 13 factors were studied in relationship to the CIN creatinine level (Table 5).

Table 5: Risk Factors and CIN Creatinine.

	Risk Factor and CIN Creatinine				
	Risk Factor Present		Risk Factor Not Present		
Pre-Existing Possible Risk Factor for CIN	**Average**	**StDev**	**Average**	**StDev**	**p-value**
Proteinuria	2.393	0.936	1.963	0.703	0.16
DM	2.35	1.0700	2.103	0.065	0.47
ACE inhibitor	2.52	1.2900	2.086	0.604	0.36
CAD	2.175	0.7180	2.222	0.905	0.90
Gout	2.168	0.6010	2.219	0.901	0.89
CHF	1.835	0.3330	2.269	0.904	0.10
Multiple myeloma	n/a	n/a	n/a	n/a	n/a
Renal surgery	n/a	n/a	n/a	n/a	n/a
Race: African-American	2.469	0.6290			
Race: Caucasian			2.029	0.940	0.20
CKD	2.272	0.5910	2.198	0.923	0.814
HD (pre-existing)	n/a	n/a	n/a	n/a	n/a
Gender: Female	2.247	0.9600			
Gender: Male			2.113	0.5120	0.62
Pretreatment regimen					
Fluids and/or mucomyst no/yes	2.26	0.9570	2.113	0.585	0.606

Relationship of Risk Factors to Delta Creatinine: 13 factors were studied in relationship to the change in creatinine from the baseline to the CIN level (Table 6).

Table 6: Risk Factors and Delta (Baseline to CIN) Creatinine.

	Risk Factor and Delta Creatinine				
	Risk Factor Present		Risk Factor Not Present		
Pre-Existing Possible Risk Factor for CIN	**Average**	**StDev**	**Average**	**StDev**	**p-value**
Proteinuria	1.36	0.91	1.00	0.62	0.20
DM	1.33	1.04	1.11	0.58	0.49
ACE inhibitor	1.48	1.27	1.09	0.53	0.40
CAD	1.18	0.76	1.21	0.84	0.94
Gout	1.13	0.36	1.22	0.86	0.72
CHF	0.81	0.26	1.26	0.85	0.04
Multiple myeloma	n/a	n/a	n/a	n/a	n/a
Renal surgery	n/a	n/a	n/a	n/a	n/a
Race: African-American	1.33	0.55			
Race: Caucasian			1.44	0.92	0.48
CKD	1.03	0.41	1.28	0.89	0.38
HD (pre-existing)	n/a	n/a	n/a	n/a	n/a
Gender: Female	1.28	0.90			
Gender: Male			0.98	0.43	0.21
Pretreatment regimen					
Fluids and/or mucomyst no/yes	1.20	0.93	1.11	0.50	0.60

Increase creatinine (delta) over baseline, comparing highest quartile of increase [> 75th percentile] to the < 75th percentile change group: As noted above, there were no patients in the study who went on to RRT.

Another endpoint was to analyze the cohort with the highest absolute increase in creatinine over baseline (> 75th percentile) to those with a lower increase in creatinine over baseline (< 75th percentile). The difference between these two cohorts, (< 75th percentile, > 75th percentile) in reference to the increase in creatinine over baseline, is statistically significant. (p = .004) (Table 7).

Table 7: Increase (delta) creatinine over baseline, comparing (> 75th percentile) to those with a lower increase in creatinine over baseline (< 75th percentile).

	Increase (delta) creatinine over baseline				
	< 75th percentile (n = 23)		≥ 75th percentile (n = 8)		
All	N	Creat	N	Creat	p-value
	23	average delta=0.856 StDev=.315	8	average delta=2.208 StDev1.23	0.004

Increase creatinine (delta) over baseline, comparing highest quartile of increase [>75th percentile] to the < 75th percentile change group: Analysis of Risk Factors: 13 factors were studied comparing highest quartile of increase [>75th percentile] to the < 75th percentile change group (Table 8). The baseline measures of age, ED creatinine, MDRD, C-G, and weight were not statistically different in comparison of the two groups. ED creatinine and age was higher in the < 75th percentile increase group (Table 9).

Table 8: Increase (delta) creatinine over baseline, comparing (> 75th percentile) to those with a lower increase in creatinine over baseline (< 75th percentile): Relationship to risk factors.

	Increase (delta) creatinine over baseline				
	< 75th percentile (n = 23)		≥ 75th percentile (n = 8)		
Pre-Existing Possible Risk Factor for CIN	Count	Present (%)	Count	Present (%)	p-value
Proteinuria	13	56%	5	62%	0.77
DM	11	48%	3	38%	0.61
ACE inhibitor	6	26%	3	37%	0.56
CAD	4	17%	2	25%	0.66
Gout	4	17%	0	0%	0.03
CHF	4	17%	0	0%	0.03
Multiple myeloma	0	0%	0	0%	1.00
Renal surgery	0	0%	0	0%	1.00
Race: African-American	7	30%	3	38%	0.72
Race: Caucasian	16	70%	5	63%	0.72
CKD	6	26%	0	0%	<.01
HD (pre-existing)	0	0%	0	0%	n/a
Gender: Female	15	65%	0	0%	
Gender: Male	8	35%	8	100%	<.01
Pretreatment regimen					
Fluids and/or mucomyst	16	69%	5	63%	0.72

Table 9: Increase (delta) creatinine over baseline, comparing (> 75th percentile) to those with a lower increase in creatinine over baseline (< 75th percentile).

	Increase (delta) creatinine over baseline				
	<75th percentile (n=23)		≥75th percentile (n = 8)		
Baseline Measures	Average	StDev	Average	StDev	p-value
Age	78.52	6.8	77.13	3.98	0.42
MDRD	53.52	8.47	55.5	7.13	0.53
C-G	57.4	17.3	71.6	36.3	0.32
ER Creatinine	1.041	0.0266	0.912	0.333	0.35
Weight(kg)	81.8	28.1	93.9	17.8	0.18

Percent increase in creatinine (delta) over baseline, comparing highest quartile of increase [> 75th percentile] to the < 75th percentile change group: As noted above, there were no patients in the study who went on to RRT.

Another endpoint was to analyze the cohort with the highest percent increase in creatinine over baseline (> 75th percentile) to those with a lower percent increase in creatinine over baseline (< 75th percentile). The average percent increase for the < 75th percentile group was 84%, StDev 32%. The average increase for the > 75th percentile group was 289%, StDev 117%. The difference between these two cohorts, (< 75th percentile, > 75th percentile) in reference to the percent increase in creatinine over baseline, is statistically significant. (p = .004).

Percent increase in creatinine (delta) over baseline, comparing highest quartile of increase [> 75th percentile] to the < 75th percentile change group: Analysis of Risk Factors from Literature and Baseline Measures: 13 factors were studied. For three factors, the analysis reflected that there were no cases present in the cohort who had the risk factors of multiple myeloma, renal surgery or pre-existing hemodialysis status).

In respect to proteinuria, DM, gout, CHF and CKD, the risk factor tracked with a higher presence (percent present) in the lower increase creatinine group. This difference was statistically significant with gout CHF and CKD (gout p = 0.03, CHF p = 0.03, CKD p = 0.01) (Table 10). The baseline measures of age, ED creatinine, MDRD, C-G, and weight were not statistically different in comparison of the two groups. *ED creatinine and age was higher in the < 75th percentile increase group* (Table 11).

Table 10: Percent increase in creatinine (delta) over baseline, comparing highest quartile of increase [> 75th percentile] to the < 75th percentile change group: Risk Factors.

	% increase creatinine over baseline				
	<75th percentile		≥75th percentile		
Pre-Existing Possible Risk Factor for CIN	**Count**	**Present (%)**	**Count**	**Present (%)**	
Proteinuria	14	58.33%	4	57.14%	0.95
DM	11	45.83%	3	42.86%	0.89
ACE inhibitor	6	25%	3	42.00%	0.39
CAD	4	16.00%	2	28.00%	0.52
Gout	4	16.00%	0	0.00%	0.03
CHF	4	16.00%	0	0.00%	0.03
Multiple myeloma	0	0%	0	0.00%	n/a
Renal surgery	0	0%	0	0.00%	n/a
Race: African-American	7	29%	3	43.00%	0.51
Race: Caucasian	17	71%	4	57.00%	0.51
CKD	6	25%	3	0.00%	0.01
HD (pre-existing)	0	0%	0	0%	n/a
Gender: Female	16	67%	7	100.00%	<.01
Gender: Male	8	33%	0	0.00%	<.01
Pretreatment regimen					
Fluids and/or mucomyst	16	66%	5	71.00%	0.80

Table 11: Percent increase in creatinine (delta) over baseline, comparing highest quartile of increase [> 75th percentile] to the < 75th percentile change group: Baseline measures.

	% increase creatinine over baseline				
	<75th percentile		≥75th percentile		
Baseline Measures	**Average**	**StDev**	**Average**	**StDev**	**p-value**
Age	78.52	6.65	76.86	4.22	0.43
MDRD	53.04	8.61	57.43	4.96	0.11
C-G	57.8	17.10	72.1	39.2	0.38
ER Creat	1.05	0.27	0.857	0.317	0.18
Weight(kg)	83.6	28.80	89.6	14	0.46

DISCUSSION

Contrast-induced nephropathy (CIN) is a disease entity that affects clinical decision making on a daily basis, given the large number of CT scans that are ordered as part of the practice of emergency medicine. CIN is an unpredictable disease, in which prevention and treatment strategies have yet to be proven fully effective. The primary goal of this study was to study a geriatric population, and determine, overall, the incidence of dialysis as a result of CIN.

Based on the definition of CIN, this disease entity is self-limiting, and the incidence of CIN requiring hemodialysis (HD) is low, yet the potential of CIN has a huge clinical impact on decision making in the emergency department. As a secondary goal, we took those patients who developed CIN, and isolated the risk factors, based on our literature review, to determine which factors had a significant impact.

This study had 31 total participants, all of whom met the definition of CIN based on our criteria above. The mean initial (baseline ED, pre-contrast) creatinine was 1.0. The minimum creatinine was 0.42, and the maximum was 1.6, with no gender significance. Post CIN creatinine, measured as the highest measured serum creatinine post-CIN diagnosis, showed a mean of 2.21, the minimum was 1.15, and the maximum was 5.5. All of these IV contrast studies were completed in the emergency department, but the type of contrast study varied, with the majority being CT Chest and CT Abdomen and Pelvis. There is no data on type or amount of contrast used.

The mean age was 78.16 years, youngest being 70 and oldest being 96. The primary outcome that we studied showed that none of our patients required dialysis as a result of the CIN. The incidence of CIN and CIN-induced hemodialysis varies in the literature due to definition changes and types of contrast used over the years. Most of the recent literature shows that in patients without risk factors, the incidence of CIN is around 2%. Those with risk factors, such as diabetes, that number may rise to as much as 9%. The incidence of renal replacement therapy (HD) in those with CIN is less than 1%, but may rise to 3.1% in those with underlying chronic kidney disease [5,6]. The results were remarkable in that none of our geriatric cohort of patients received HD as a result of the CIN from ER related contrast studies. And as importantly, none of the patients were on dialysis previously.

What factors could explain this finding? Gender has not been identified as a risk factor, and in our study, the majority of participants were female. The data suggest that this does not explain the results, since gender is not associated with any differences in outcomes of CIN. While African Americans with diabetic nephropathy have a faster acceleration of end-stage renal disease (ESRD), independent of other variables, race has not been found to be a risk factor for CIN [7]. There were no statistically significant differences between races in this study. Also, weight played a factor only in determining the C-G equation. Weight or BMI has not been established as a risk factor or determinant for CIN[7]. In the study, weights by gender and weights by race were not statistically significant.

The CIN cohort in this study was analyzed in reference to risk factors determined from a review of the literature 9 factors were reviewed (see above). There were no cases of multiple myeloma or previous renal surgery (i.e. transplant or nephrectomy). Of the remaining 7 factors, five were statistically different with p-values less than 0.05, all in the direction of more likely *absent* than present. They were: being on an ACE inhibitor, having pre-existing chronic kidney disease, having a history of coronary artery disease, gout, and congestive heart failure. So, *overall, the study population did not have statistically significant risk factors for developing CIN, but instead, had statistically significant lack of risk factors for developing CIN, with the exception of diabetes mellitus and proteinuria, which were not statistically different.* Pre-existing CKD has been linked to the greatest risk of developing CIN compared to all other risk factors [4]. In this study, 6 patients (19.4%) had a history of CKD. The remaining 25 patients (80.6%) did not. This difference was statistically significant.

When each risk factor was examined separately in relation to CIN creatinine, there was no significant difference in relation to individual risk factors. What was an interesting trend, was that CAD, gout, and CHF had tendencies toward a *higher* CIN creatinine in the direction of a higher CIN in the absence of CAD, gout and CHF. This finding appears to be previously unreported in the literature. A PUBMED search failed to find any prior documented evidence that showed having a risk factor for CIN in the geriatric population caused a smaller increase in CIN creatinine.

The most influential factor in preventing CIN is to restore a euvolemic state [4]. Most cases of CIN are a result of underlying pre-renal azotemia from an underlying disease state, with CIN resulting from diagnosing that disease entity or ruling out other disease entities as the potential cause of presenting symptoms. In this study, the data showed that 21 patients (67.7%) received pretreatment and 10 patients (32.3%) received no pretreatment, which were different statistically ($p = .003$). The majority received pretreatment which was, generally speaking, a bolus of varying amounts of normal saline. Some of those that did not receive a pretreatment strategy were mostly presentations or disease concerning for hyper-

volemia. Although statistically different, when looking at the data and cases closely, this supports the current literature based proposition that pretreating to a euvolemic state will help reduce effects of CIN.

The methods that are currently available to estimate glomerular filtration rates (eGFR) were compared. Our hospital system has used the MDRD equation, and this equation is now the accepted equation to estimate GFR; however, the Cockcroft-Gault (C-G) formula, which has multiple versions, was once used to estimate creatinine clearance. Novel serum markers are being developed, all of which appear to have limitations in estimating GFR [8].

In our study, MDRD and C-G did not statistically correlate with each other, with a Pearson correlation of 0.269 and a p-value of 0.143. The MDRD showed good correlation with the ED creatinine, in the direction of a lower MDRD tracking with a higher ED creatinine (negative correlation). The C-G also correlated with the ED creatinine, but more weakly than the MDRD. This exemplifies the current reasoning behind MDRD being the most trusted estimate of GFR as it has a higher correlation. The finding that MDRD and C-G did not correlate with each other has been seen in other studies comparing estimates of GFR [9-11]. It has been found that as the age of a person increases, the correlation of MDRD to C-G decreases. Newer markers of eGFR are being developed, due to the finding that in the geriatric population, MDRD and C-G demonstrate a declination in accuracy in measuring eGFR in older patients. When comparing MDRD to C-G with percent change in creatinine overall, MDRD showed no statistical difference where C-G was statistically different. This, again, reiterates the point that C-G formula is a less accurate estimator of GFR.

As shown in the literature, disease states play a factor in determining eGFR, where the accuracy of eGFR decreases if a patient has an acute condition [8]. When measuring the post-CIN creatinine in our study, neither the MDRD nor the C-G showed statistically significant correlation with the CIN creatinine. The MDRD was superior in its correlation, but still not statistically significant. Neither the MDRD nor the C-G showed good correlation with the absolute increase (delta) between the ED creatinine and the CIN creatinine. Neither the MDRD nor the C-G showed good correlation with the percent increase between the ED creatinine and the CIN creatinine. The admitting diagnoses fell into 24 separate categories, most frequently pneumonia, shortness of breath, and small bowel obstruction, followed by COPD exacerbation. The final diagnoses comprised 26 discrete diagnoses. We were unable to correlate a specific diagnosis with CIN; however, the importance of an acute disease state affecting the measurement of eGFR has been illustrated.

A frail elderly (> 85 years of age) sub-cohort was analyzed. The ≥ 85 year old patient cohort showed a statistically significant higher baseline creatinine. However, the change in CIN creatinine was higher in the 70-84 year old age group, but not statistically significant. The interesting finding here was that the older group had a higher creatinine at baseline, which one might expect with an acute process, but a smaller change in creatinine after CIN which one would not expect. The hypothesis that may be drawn from this finding is that it is possible that the geriatric kidney, in the frail elderly age group (≥ 85), might be protected from the effects IV contrast. The pathophysiology behind CIN is theorized to be primarily due to renal ischemia event with several cascaded events, as discussed in the background statement. Is it possible that the geriatric kidney, in the frail elderly has an inherent resistance to CIN based on years of insult and adaptability? Is it possible that the geriatric kidney is without enough renal medulla to illicit a response to such an ischemic event? Current literature search has proven lack of any evidence to support this question or deny its inferences. One of the authors of this study, (JE) has referred to this study observation as the "Baird Hypothesis."

The highest quartile (> 75th percentile) in absolute change was assessed to determine the characteristics of that patient group. The average increase from baseline creatinine was 2.21. The difference when compared to the < 75th percentile was statistically significant. When analyzing the risk factors in this comparison, the data showed that the risk factors of CKD, male gender, gout, and CHF were significantly different. The interesting finding is that male patients had an increased risk of being in the > 75th percentile, but the other risk factors were associated with being in the < 75th percentile. Also, having the above risk factors appears to place them in a category of less change in creatinine.

The upper quartile (> 75th percentile) of percent change was specifically analyzed. In examining all the risk factors, in the cohorts of DM, gout, CHF and CKD, the risk factor tracked with a higher presence (percent present) in the lower increase creatinine group. This difference was statistically significant with gout, CHF, and CKD. This correlates with the previous finding that having those risk factor placed the patient in a lower percent change group.

This study was limited to the geriatric population in a three hospital systems.

It is possible that these results may not be generalizable.

CONCLUSION

Contrast-induced nephropathy, by definition, is a self-limiting disease. However, there is still great concern by ED physicians to avoid causing CIN in their elderly patients. Fear of causing damage to the kidneys could lead to utilizing less accurate diagnostic tests. The results of the patient cohort in this study showed that the incidence of CIN in the geriatric population studied requiring dialysis was 0%. Risk factors did not play a major role in causing a larger change from baseline creatinine. Risk factors did not play a major role in causing a larger percent change. Lastly, the geriatric kidney might have a counter-intuitive protective effect from IV contrast for an as yet unknown reason. It appears, according to our study, that the older the kidney, the better that kidney tolerated IV contrast. Two of the authors of this study, (JE, VS) have referred to this hypothesis as the "Baird Hypothesis." This study was limited to the geriatric population in a three hospital systems. It is possible that these results may not be generalizable.

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