High Dose Intravenous Vitamin C Treatment in Sepsis: Associations with Acute Kidney Injury and Mortality Running Title Vitamin C associated AKI and mortality

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Abstract

The effects of vitamin C on clinical outcomes in critically ill patients remain controversial due to inconclusive studies. This retrospective observational cohort study evaluated the effects of vitamin C therapy on acute kidney injury (AKI) and mortality among septic patients. Participants were 1390 patients from an academic hospital who were categorized as Treatment (received at least one dose of 1.5g IV vitamin C, $n = 212$) or Comparison (received no, or less than 1.5g IV vitamin C, $n = 1178$). Propensity score matching was conducted to balance a number of covariates between groups. Multivariate logistic regressions were conducted predicting AKI and in-hospital mortality among the full sample and a sub-sample of patients seen in the ICU. Results revealed that vitamin C therapy was associated with increases in AKI (OR = 2.07 95% CI [1.46–2.93]) and in-hospital mortality (OR = 1.67 95% CI [1.003–2.78]) after adjusting for demographic and clinical covariates. When stratified to examine ICU patients, vitamin C therapy remained a significant risk factor of AKI (OR = 1.61 95% CI [1.09–2.39]) and provided no protective benefit against mortality (OR = 0.79 95% CI [0.48–1.31]). Ongoing use of high dose vitamin C in sepsis should be appraised due to observed associations with AKI and death.

Clinical Summary

- Existing research regarding the effect of vitamin C on outcomes in patients with sepsis is inconsistent.
- This retrospective study of patients hospitalized for sepsis revealed an association between IV vitamin C usage and subsequent AKI and in-hospital mortality.
- The relationship between early treatment of high dose IV vitamin C and mortality in septic patients might suggest potential nephrotoxicity of vitamin C therapy.
- Findings, coupled with results from multiple randomized controlled prospective studies of IV vitamin C with mixed results, suggests that wide-spread use of high dose IV vitamin C requires further assessment.

Introduction

The benefits of ascorbic acid (vitamin C) therapy were first noted in the 1970s, related to infections and the common cold (1). The unique set of physiological properties of vitamin C have given its use promise in decelerating a multitude of different forms of infection. Vitamin C serves to protect host cells from oxidative damage during the inflammatory response through its role as an antioxidant (2), it preserves other endogenous antioxidants, including lipid soluble vitamin E and glutathione (3), and it has been shown to contribute to bactericidal activity via augmentation of T-cell and neutrophil function (4). As plasma vitamin C is quickly depleted during severe inflammatory states, vitamin C has emerged as a possible adjuvant therapy in sepsis (5, 6).

Sepsis remains a major public health issue as the 10th leading cause of death among non-Hispanic black individuals and 12th among non-Hispanic white individuals in the U.S., and infecting more than

1.7 million U.S. Americans annually (7, 8). Within the hospital setting, sepsis remains a significant concern with mortality rates above 50% and over \$24 billion dollars spent each year on sepsis-related hospitalizations (9–13). Identifying effective and appropriate treatments to reduce sepsis-related mortality and hospital length of stay (LOS) remains a challenge.

Early examinations of vitamin C supplementation, alone or in combination with thiamine (vitamin B1) and corticosteroids, revealed decreased inflammatory markers and end-organ dysfunction (14, 15). Extant research, however, is inconsistent regarding the effect of vitamin C on outcomes in patients with sepsis. Of six randomized controlled trials, only two found improvement in patient markers such as SOFA score, vasopressor requirement, and lactate levels (14, 16–20). Only one study found reduced likelihood of mortality with vitamin C therapy; however, notably, this study did not find improvement in SOFA score (17). Observational studies also remain mixed. One of three retrospective and quasi-experimental studies found improvements in both mortality and markers of patient stability, a second found a reduction in mortality but no benefit for markers of stability, and a third found no benefit of mortality or markers of stability (15, 21, 22).

Given the contradictory findings in both RCTs and observational studies, more research is needed to ascertain the effects of vitamin C therapy among septic patients. In the current study, a retrospective analysis was conducted to investigate the relationship of intravenous (IV) vitamin C on acute kidney injury (AKI) and mortality among patients with sepsis.

Materials And Methods

Clinical Order Set

In August 2016, a sepsis vitamin order set was formalized but not mandated in the hospital in which the study was completed. The decision to utilize the order set was up to the individual provider. The order panel included IV vitamin C at a dose of 1.5g, administered every 6 hours for a maximum of 16 doses; IV hydrocortisone 50mg every 6 hours up to 28 doses; and IV thiamine 200mg every 12 hours for 8 doses. In December 2018, melatonin 0.5mg at bedtime was added to the order set with no stop required. The order panel did not include diagnostic studies to determine the severity of sepsis nor did it include treatment option directions based on clinical parameters.

Study Design

This retrospective cohort study was conducted at a tertiary care, academic hospital and was approved by the EVMS Institutional Review Board. Adult patients, age 18 through 89 years, with International Classification of Disease (ICD)-10 code for “sepsis”, admitted between August 1, 2016 and December 31, 2018, were identified via electronic health records (EHR-Epic Systems Corporation, Verona, WI, USA). Inclusion criteria included (1) admission via the ED, (2) hospitalization for at least 48 hours, and (3) two serum creatinine assays 48 hours apart. ED admission was required in order to capture patients with community acquired infections and limit those with sepsis after nosocomial infections, post-surgical

sepsis, and transfer patients who may have missed the opportunity for early vitamin C therapy. These factors have been identified as potential confounders of treatment effectiveness, as nosocomial infections may be more likely to be drug resistant and more difficult to treat (23). Patients with admission glomerular filtration rates less than 35ml/min (measured by the Modification of Diet in Renal Disease (MDRD) formula (24)), an initial creatinine greater than 4.0mg/dL, or a diagnosis of end stage kidney disease or prior kidney transplant were excluded from the study.

The following data were collected from the EHR: patient demographics; past medical history; visit characteristics (i.e., pre-identified medications administered, laboratory results, order sets ordered); primary and secondary diagnoses; hospital and ICU LOS; vasoactive drug use; and in-hospital mortality. Vasoactive drug use was defined as having received Dobutamine, Dopamine, Epinephrine, Norepinephrine, Phenylephrine, or Vasopressin. AKI was defined using ICD-10 code discharge diagnoses. Doses of IV vitamin C received were captured to categorize patients into two groups; comparison group (No or < 1.5g of IV vitamin C), and treatment group (≥ 1.5 g of IV vitamin C within 12 hours of hospital admission). Individuals who received ≥ 1.5 g of IV vitamin C more than 12 hours after hospital admission were excluded from the study as research suggests that vitamin C treatment after the first 12 hours may not be as efficacious (25). Of note, two patients in the comparison group received low doses of IV vitamin C of 0.5 g or less.

Statistical Analysis Plan

To assess bivariate associations, categorical data were compared using chi-square or Fisher's exact test when appropriate, and continuous data were analyzed using independent-samples t-tests. Preliminary analyses revealed statistically significant demographic differences between individuals in the treatment versus comparison groups (Table 2). In order to balance the covariate distribution between groups, propensity score matching (PSM) was performed on the overall population using the following variables: insurance, race, biological sex, history of diabetes, history of hypertension, vasoactive drug use, and patient age. The greedy method for matching was performed using a 3:1 ratio (comparison: treatment) to best match the groups' sample size of the full study population. Using the matched sample, preliminary bivariate associations with primary outcome variables (i.e., AKI, mortality) were conducted and statistically significant and clinically meaningful variables were entered into two multiple logistic regressions. As the majority of patients (96%) who received high dose IV vitamin C were admitted to the ICU, subsequent analyses were conducted on the sub-sample of ICU patients. Similar to the full population, PSM using the aforementioned variables was performed to balance between treatment and comparison groups who were seen in the ICU, with matching performed using a 2:1 ratio (comparison: treatment) to match the ICU groups' sample sizes. Preliminary bivariate analyses and multiple logistic regressions were then conducted on the ICU sample predicting AKI and mortality. A p -value of less than 0.05 and 95% confidence intervals (CI) not including one were considered significant. All analyses were performed using SAS 9.4 software.

Table 2
Bivariate Analyses between IV Vitamin C Group and Comparison Group

All Patients (n = 1390)			
Demographic Characteristic	IV vitamin C (n = 212)	Comparison (n = 1178)	p
Continuous	μ ± SE	μ ± SE	
Age (years)	62 ± 1.15	59 ± 0.51	0.02
Length of Stay (hours)	302 ± 18	319 ± 13	0.44
Length of Stay in ICU (hours)	119 ± 10	76 ± 6	< 0.001
Categorical	n (%)	n (%)	p
Insurance Status			
Government	182 (86)	893 (76)	0.001
Other	30 (14)	285 (24)	
Race			
Black	118 (56)	611 (52)	0.57
White	84 (39)	500 (42)	
Other/Unknown	10 (5)	67 (6)	
Biological Sex			
Female	100 (47)	542 (46)	0.76
Male	112 (53)	636 (54)	
Hypertension			
Yes	71 (33)	454 (39)	0.16
No	141 (67)	724 (61)	
Diabetes			
Yes	17 (8)	112 (10)	0.49
No	195 (92)	1066 (90)	
Vasoactive Drug Use*			

AKI = Acute Kidney Injury

*Vasoactive drug use was defined as having received at least one of the following: Dobutamine, Dopamine, Epinephrine, Norepinephrine, Phenylephrine, or Vasopressin

All Patients (n = 1390)			
Yes	36 (17)	193 (16)	0.83
No	176 (83)	985 (84)	
AKI			
Yes	145 (68)	550 (47)	< 0.001
No	67 (32)	628 (53)	
Death			
Yes	30 (14)	89 (8)	0.002
No	182 (86)	1089 (92)	
AKI = Acute Kidney Injury			
*Vasoactive drug use was defined as having received at least one of the following: Dobutamine, Dopamine, Epinephrine, Norepinephrine, Phenylephrine, or Vasopressin			

Results

Sample Demographics and Descriptives

Of the 26,346 patient admissions between 1 August 2016 and 31 December 2018, 16,159 were admitted via the ED. Of the ED admissions, 1390 were identified as having a diagnosis of sepsis based on 42 ICD-10 codes and were included for analysis. Overall, diagnosis of AKI and in-hospital mortality rates were 50% and 9%, respectively. Patients were primarily male (54%), identified as black (52%) or white (42%), and had an average age of 59 years. The majority of patients had government insurance (77%), 38% and 9% of patients had a diagnosis of hypertension and diabetes, respectively, and 16% of patients received vasoactive drugs during their visit (see Table 1). Of the 1390 patients, 212 (15%) were identified as part of the IV vitamin C treatment group and 1178 (85%) were considered part of the comparison group. Within the treatment group, patients received high dose IV vitamin C, on average, 4.58 hours after admission.

Table 1
Overall Descriptive Statistics (n = 1390)

Continuous Variables	$\mu \pm SE$
Age (years)	59 $\pm$ 0.46
Length of Stay (hours)	316 $\pm$ 11
Length of Stay in ICU (hours)	82 $\pm$ 5
Categorical Variables	n (%)
Insurance Status	
Government	1075(77)
Other	315(23)
Race	
Black	729(52)
White	584(42)
Other/Unknown	77(6)
Biological Sex	
Female	642(46)
Male	748(54)
Hypertension	
Yes	525(38)
No	865(62)
Diabetes	
Yes	129(9)
No	1261(91)
Vasoactive Drug Use*	
Yes	229 (16)
No	1161 (84)
IV vitamin C Use	

AKI = Acute Kidney Injury

*Vasoactive drug use was defined as having received at least one of the following: Dobutamine, Dopamine, Epinephrine, Norepinephrine, Phenylephrine, or Vasopressin

Continuous Variables	$\mu \pm SE$
Yes	212(15)
No	1178(85)
AKI	695(50)
Yes	695(50)
No	
Death	
Yes	119(9)
No	1271(91)
AKI = Acute Kidney Injury	
*Vasoactive drug use was defined as having received at least one of the following: Dobutamine, Dopamine, Epinephrine, Norepinephrine, Phenylephrine, or Vasopressin	

Bivariate analyses revealed that individuals in the IV vitamin C group were slightly older (61 years versus 58 years, $p = 0.02$), had longer ICU LOS (119 hours versus 76 hours, $p < 0.001$), were less likely to have a history of hypertension (33% versus 39%, $p = 0.02$), more likely to have AKI (68% versus 47%, $p < 0.001$), and more likely to have died in the hospital (14% versus 8%, $p = 0.002$) compared to those in the comparison group (see Table 2). Given the differences between treatment and comparison groups, PSM was performed to balance covariates. The 3:1 matching reduced the full sample to $N = 848$ and the ICU group 2:1 matching reduced the ICU sample to $N = 534$. After PSM, preliminary analyses revealed that the treatment group was more likely to develop AKI (68% versus 49%, $p < 0.001$) and more likely to have died in the hospital (14.15% versus 8.02%, $p = 0.01$). Results of the multivariate logistic regressions are described below.

Acute Kidney Injury. A multivariate logistic regression determining adjusted odds ratio (AOR) revealed that age (AOR: 1.03 95%CI: 1.02–1.04), ICU LOS (AOR: 1.003 95%CI: 1.001–1.004), race (i.e., black compared to white; AOR: 1.59 95%CI: 1.12–2.16), sex (i.e., female compared to male; AOR: 0.70 95%CI: 0.52–0.93), and IV vitamin C (AOR: 2.07 95%CI: 1.46–2.93) were associated with an increased likelihood of AKI. Other covariates including insurance, hypertension, diabetes, and vasoactive drug use were not significant. See Table 3a.

Table 3

Multiple Logistic Regression Models Predicting Acute Kidney Injury and Mortality in the Total Population Performed after Propensity Score Matching (3:1) (n = 848)

a. Acute Kidney Injury			b. Mortality	
Variable	Adjusted-OR (95% CI)	p-value	Adjusted-OR (95% CI)	p-value
Age (years)	1.03 (1.02, 1.04)	< 0.001	1.03 (1.01, 1.05)	0.007
Length of ICU Stay (hours)	1.003 (1.001, 1.004)	< 0.001	1.002 (1.001, 1.003)	< 0.001
Insurance (ref = Other)	0.78 (0.51, 1.21)	0.27	1.03 (0.44, 2.39)	0.95
Race (ref = White)	1.59 (1.18, 2.16)	0.04	1.31 (0.78, 2.20)	0.64
Black	1.14 (0.58, 2.24)	0.76	2.28 (0.83, 6.29)	0.16
Other/Unknown				
Biological Sex (ref = Male)	0.70 (0.52, 0.93)	0.01	0.80 (0.48, 1.32)	0.38
Hypertension (ref = No)	0.78 (0.57, 1.07)	0.12	1.30 (0.77, 2.20)	0.33
Diabetes (ref = No)	0.85 (0.50, 1.45)	0.55	0.87 (0.33, 2.33)	0.78
Vasoactive Drug Use* (ref = No)	1.54 (0.98, 2.40)	0.06	1.46 (0.81, 2.63)	0.21
IV vitamin C (ref = No)	2.07 (1.46, 2.93)	< 0.001	1.67 (1.003, 2.78)	0.04
AKI			3.21 (1.70, 6.03)	< 0.001
AKI = Acute Kidney Injury				
*Vasoactive drug use was defined as having received at least one of the following: Dobutamine, Dopamine, Epinephrine, Norepinephrine, Phenylephrine, or Vasopressin				

Mortality. A multivariate logistic regression predicting mortality revealed that age (AOR: 1.03 95%CI: 1.007–1.05), ICU LOS (AOR: 1.002 95% CI: 1.001–1.003), diagnosis of AKI (AOR: 3.21 95%CI: 1.70–6.03), and IV vitamin C (AOR: 1.67 95% CI: 1.003–2.78) were associated with in-hospital mortality. Insurance, race, hypertension, diabetes, and vasoactive drug use were not significant. See Table 3b.

Sub-Analysis on ICU Patients Only (n = 534)

Acute Kidney Injury. A multivariate logistic regression performed on the sub-set of individuals who spent time in the ICU found that age (AOR: 1.02 95% CI: 1.01–1.04), ICU LOS (AOR: 1.003 95% CI: 1.001–1.004), and IV vitamin C (AOR: 1.61 95% CI: 1.09–2.39) were significant predictors of AKI. All other covariates were not significant. See Table 4a.

Table 4
Multiple Logistic Regression Models Predicting Mortality and Acute Kidney Injury in the ICU Population
Performed after Propensity Score Matching (2:1) (n = 534)

a. Acute Kidney Injury			b. Mortality	
Variable	Adjusted-OR (95% CI)	p-value	Adjusted-OR (95% CI)	p-value
Age (years)	1.02 (1.01, 1.04)	< 0.001	1.03 (1.007, 1.04)	0.01
Length of ICU Stay (hours)	1.003 (1.001, 1.004)	< .001	1.001 (1.000, 1.002)	0.05
Insurance (ref = Other)	0.93 (0.56, 1.54)	0.78	1.51 (0.68, 3.33)	0.31
Race (ref = White)	1.47 (0.99, 2.19)	0.04	1.56 (0.94, 2.60)	0.85
Black	0.71 (0.28, 1.78)	0.24	2.77 (0.88, 8.73)	0.16
Other/Unknown				
Biological Sex (ref = Male)	0.77 (0.52, 1.12)	0.17	0.67 (0.41, 1.11)	0.12
Hypertension (ref = No)	0.72 (0.49, 1.08)	0.11	1.18 (0.70, 1.96)	0.54
Diabetes (ref = No)	1.39 (0.68, 2.83)	0.37	0.47 (0.16, 1.38)	0.17
Vasoactive Drug Use* (ref = No)	1.37 (0.84, 2.24)	0.20	0.90 (0.50, 1.63)	0.72
IV vitamin C (ref = No)	1.61 (1.09, 2.39)	0.02	0.79 (0.48, 1.31)	0.36
AKI			2.01 (1.12, 3.59)	0.02
AKI = Acute Kidney Injury				
*Vasoactive drug use was defined as having received at least one of the following: Dobutamine, Dopamine, Epinephrine, Norepinephrine, Phenylephrine, or Vasopressin				

Mortality. A multivariate logistic regression revealed that age (AOR: 1.03 95% CI: 1.01–1.04) and AKI (AOR: 2.01 95% CI: 1.12–3.59) were significant predictors of in-hospital mortality. All other variables in the regression analysis, including IV vitamin C, were not significant. See Table 4b.

Discussion

This retrospective study of patients hospitalized for sepsis revealed an association between IV vitamin C usage and subsequent AKI and in-hospital mortality. When examining the association of IV vitamin C therapy and AKI, the odds of experiencing AKI for individuals treated with IV vitamin C were 107% higher than the odds for individuals not treated with IV vitamin C, after controlling for a number of demographic and clinical variables. Findings also revealed that risk of AKI was increased for those who were male and older, which is supported in previous research (26, 27). Findings are consistent with results from a similar

study of patients admitted via the ED for sepsis, which found that individuals over 65 years were at significantly higher risk of AKI and subsequent in-hospital death (28). Other research has also highlighted the relationships between increased LOS and older age, and the occurrence of AKI and mortality (29, 30). Other notable factors in the current study associated with increased risk of AKI were longer ICU LOS and identifying as black as compared to white, both of which are risk factors supported by previous research (34–36). The association between IV vitamin C and AKI is not unique to this study; a study by Litwak et al. observed a 12% increase in AKI in patients that received IV vitamin C but this did not reach statistical significance, likely due to small sample size (22).

When examining in-hospital mortality, results revealed that being older, having AKI, longer ICU LOS, and receiving IV vitamin C were associated with increased risk of mortality. Specifically, the odds of mortality were 67% higher for the IV vitamin C group compared to those in the comparison group. The association between high dose vitamin C and death was unexpected and not easily explained. Another variable found to be associated with an increased risk of death, which may lend insight into the relationship between vitamin C and mortality, was the diagnosis of AKI. Previous research indicates kidney failure increases the risk of death six to eight times in septic patients (37). However, when examining the data in the current study, an increased risk of death was evident irrespective of AKI. Among patients who did not have AKI and did not receive IV vitamin C, 3.03% died compared to 7.46% of those who did not have AKI but received IV vitamin C. This suggests there may be a direct effect of high dose vitamin C that may exacerbate the risk of mortality. The current study lacked the data that would allow for a more comprehensive examination between high doses of IV vitamin C and potential increased toxicity outside of the kidney, however, future research should explore the relationship between vitamin C and mortality, irrespective of AKI.

The current finding that IV vitamin C is associated with increased risk of death is inconsistent with another large retrospective study which found IV vitamin C to be associated with reduced mortality among patients with sepsis (21). One reason for the disparate results may be differences in treatment dose. Specifically, vitamin C in the Byerly et al. study was not limited to high dose and was not defined by a threshold defining the treatment group, whereas the current study examines what is considered *high dose* IV vitamin C ($\geq 1.5\text{g}$), which may account for outcome differences. One study that examined higher doses (200mg/kg/day) of vitamin C showed evidence of increasing rates of mortality, with higher mortality (50.6%) among a high dose vitamin C group compared to patients who received lower doses of vitamin C (50mg/kg/day) (38%), though both treatment groups had lower mortality than the placebo group (63%) (14). Notably, this study was limited by a small sample size and did not reach statistical significance. Additional research examining other clinical markers including SOFA scores in patients receiving high dose IV vitamin C over long periods of time is needed.

Sub-analyses of the ICU sample revealed that age, longer ICU LOS, and receiving IV vitamin C remained predictors of AKI, while identifying as black and being male were no longer significant predictors. Older age, and ICU LOS are both known risk factors supported by previous research (34–36). A second sub-analysis revealed that age and AKI remained significant predictors of in-hospital mortality, however high

dose IV vitamin C use was no longer a statistically significant predictor of mortality once the sample was limited to ICU patients only.

The current study observed a moderate relationship between IV vitamin C and mortality in septic patients, which might suggest potential nephrotoxicity of vitamin C therapy. The association between high dose vitamin C and AKI due to oxalate deposition in renal tubules is well established (38). Since early reports in 1985, there are multiple cases of AKI resulting from high dose vitamin C, administered parenterally or orally (39–43). Ascorbic acid is metabolized intracellularly and converted to oxalic acid (44); the oxalic acid is then filtered in the kidney where it precipitates into crystals of calcium oxalate, potentially causing obstruction and tubular injury. Previous research has shown that vitamin C doses as low as 480–960 mg/D, taken orally over several months, have resulted in oxalate deposition kidney failure that requires temporary dialysis (45). Dietary supplementation of 2g per day can increase oxalate excretion by 21.8% (46). Oxalic acid and oxalate toxicity have been shown to occur in myocardial tissue of patients with hereditary hyperoxaluria (47). Others have suggested that similar myocardial tissue damage can occur in secondary forms of hyperoxalosis (48, 49). Acutely elevated oxalate levels in the serum could cause myocardial dysfunction, leading to increased risk of mortality regardless of AKI.

Limitations

This study was limited in the retrospective nature of the design, which precludes causal-effect conclusions and prevents patient follow-up. Relatedly, the EHR data utilized did not include time stamps for diagnoses and treatment, thus temporal order is unknown. However, strict inclusion and exclusion criteria were applied in an effort to reduce selection bias and focus on community-acquired sepsis. Further, as vasoactive drug use and ICU admission were the only available surrogates for illness severity, these factors were considered in the PSM and sample stratification, respectively. Although the current study was limited to one hospital, the large sample size provided adequate power to detect statistically significant associations between patient-level demographic and clinical variables, and specifically, vitamin C usage, AKI, and mortality. Additionally, existing literature has commonly reported SOFA scores, which were unable to be utilized in the current study due to inconsistencies in collection. Many studies have used SOFA scores as a representation of mortality risk, whereas in the current study, we were able to directly examine in-hospital mortality as a primary outcome. Additionally, the usage of serum lactic acid and procalcitonin levels were reviewed as a potential measure of disease severity but could not be included in analyses due to data missing not at random. In other words, these laboratory tests were not performed equally across all groups of patients. Finally, the current study did not assess for other nephrotoxic drugs that could be related to AKI, such as antimicrobials and radiologic contrast dye. Future research should include these as well as other factors to assess the unique relationship between IV vitamin C and AKI.

Conclusion

This retrospective review of patients with sepsis revealed that early use of high dose IV vitamin C may increase the likelihood of AKI and does not serve as a protective factor against mortality. The association of vitamin C with AKI, along with the association of AKI and mortality in patients admitted to the ICU, suggests that high dose vitamin C may be toxic. This finding, coupled with results from multiple randomized controlled prospective studies of IV vitamin C with mixed results, suggests that wide-spread use of high dose IV vitamin C requires further assessment. Additional research utilizing existing hospital data from across the nation and worldwide are needed to better understand the relationship between high dose IV vitamin C therapy and subsequent outcomes.

Declarations

Disclosures The authors have no disclosures to report.

Ethics approval and consent to participate: This study was approved by the EVMS Institutional Board on 12 December 2019 (19-05-XX-0131). The study was exempted from full review because only fully de-identified data was provided to the researchers

Consent for publication: All data analyzed was de-identified therefore no consents are required

Availability of data and materials: All data analyzed is maintained at HADSI, EVMS, Norfolk, Virginia

Competing interests: The authors declare that they have no competing interests

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Authors' contributions:

T M(Corresponding Author) Developed the conception; design of the work; the acquisition; interpretation of data; have drafted the work; and substantively revised it.

B S Assisted in development of the conception; design of the work; analysis, interpretation of data; have drafted the work and substantively revised it.

M S Assisted in the drafting of the work and substantively revised it

S P Assisted in the drafting of the work and substantively revised it

A T **Lead the** analysis; interpretation of data;have drafted the work; and substantively revised it. **S D** **Assisted in developing the** conception; design of the work; the acquisition; analysis; interpretation of data;have drafted the work and substantively revised it

Each author has approved the submitted version.

Each author has agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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