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Research article

Vitamin D Insufficiency is Associated with a Higher Risk of In-Hospital Mortality in Critically-Injured Trauma Patients

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Abstract

Introduction

Vitamin D insufficiency has been shown to be prevalent in modern society. It has been associated with worsening outcomes in critically ill patients. However, its effect on critically injured trauma patients is unknown. We hypothesize that Vitamin D insufficiency is an independent risk factor for increased in-hospital mortality in critically injured trauma patients (CITPs) requiring admission to the intensive care unit (ICU).

Material and Methods

We prospectively followed 434 trauma patients admitted to the ICU at a large urban teaching hospital between August 2009 and February 2012. Serum Vitamin D3 levels were measured upon ICU admission. Patients were stratified into sufficient group (≥ 27 ng/mL), insufficient group (14 - 26 ng/mL) and severely insufficient (< 14 ng/mL) group and evaluated for in-hospital mortality. The secondary measure was prevalence of Vitamin D insufficiency/deficiency.

Results

The mortality rate for individuals in the deficient and insufficient groups were 7.02% and 7.69%, respectively, versus 3.64% in the sufficient cohort (p = 0.0158). The overall mortality rate was 7.39% (28/379) for those with baseline vitamin D3 levels < 27 ng/mL. This equated to 2-fold higher risk of death in CITPs who presented with inadequate vitamin D3 stores. Three hundred seventy-nine patients (87.3%) presented with 25-hydroxy-Vitamin-D3 insufficiency/deficiency and 55 patients (12.7%) demonstrated sufficient Vitamin D3 levels.

Conclusion

Vitamin D insufficiency is associated with an increased risk of in-hospital mortality in critically injured trauma patients requiring management in the surgical ICU (SICU). Improving 25-hydroxy-Vitamin D3 stores to sufficient levels in the general population may be beneficial before patients become severely injured or critically ill.

Keywords: *Vitamin D Deficiency; Trauma Patients; Critically Injured; Critical Illness; In-Hospital Mortality; Surgical Intensive Care Unit*

Introduction

Mounting evidence suggests that Vitamin D3 insufficiency is highly prevalent in both the general population and hospitalized patients [1,2]. Several studies have particularly shown that Vitamin D3 deficient states are also common in the setting of critical illness and may

be associated with acute physiologic complications, which worsen outcomes [3-10]. Depending on the level or criteria used to defined insufficient, hypovitaminosis D3 has been observed in over 50 - 80% of the general population [2,11,12,13], and at an even higher rates in hospitalized critically ill patients [3,14]. Similarly, 77.4% of the patients have been found to have deficient vitamin D3 stores in a retrospective study of 889 orthopedic trauma patients [15].

It is important to note Vitamin D3 deficiency has been correlated with an increased incidence of multiple system diseases, including myocardial infarction, cardiac failure, stroke, type I and type II diabetes mellitus, pneumonia, sepsis, and many autoimmune disorders [10,11,12]. At an organ level, vitamin D3 insufficiency may result in increased risk of cardiac dysfunction, renal dysfunction and acute lung injury in critically injured patients [12,16,17,18]. Furthermore, suboptimal Vitamin D3 states have been shown to be an independent risk factor for falls and fractures among the elderly [15,19]. Consequently, critically ill surgical and medical patients requiring management in the ICU have been demonstrated to have a higher risk of mortality and untoward outcomes related to their suboptimal Vitamin D3 status [3-10]. Extensive, ongoing research has been undertaken to elucidate the etiology of these findings.

Several studies have shown increased risk for mortality and complications in mixed populations of surgical ICU patients [3,5,6,7]. However, the adverse effect of inadequate Vitamin D3 levels on the outcomes of severely injured, critically-ill trauma patients necessitating admission to the ICU has not been clearly established.

Therefore, little evidence guides clinicians in the management of Vitamin D3 deficiency in the setting of critical illness in severely injured trauma patients admitted to the ICU. Considering the numerous actions of Vitamin D3 on immunity, metabolic function and mineral homeostasis, Vitamin D inadequacy may or may not be a fundamental contributor to the excess morbidity and mortality observed in a subset of critically ill trauma patients. In particular, those that develop infections, systemic inflammatory response syndrome (SIRS), sepsis, multisystem organ failure, and metabolic syndrome may be at increased risk [3-10]. In fact, epidemiological findings suggest that Vitamin D deficiency may be an independent risk factor for sepsis [20,21]. Similarly, in critically ill trauma patients, Vitamin D insufficiency may lead to immune dysfunction, which may manifest as an exaggerated SIRS response or increased susceptibility to nosocomial infections, including ventilator associated pneumonia (VAP), central line-associated blood stream infections (CLABSI), urinary tract infections (UTIs), and septicemia [20,21].

The significance of this study is that it evaluates and elucidates the effect of Vitamin D inadequacy in critically ill trauma patients managed in the ICU on patient outcomes. A correlation has been noted between increased mortality and Vitamin D deficiency in the general population [12], which may be amplified in the setting of critical illness. This could help explain the increased risk of morbidity and mortality associated with Vitamin D3 insufficiency reported by some authors [3-10]. Insufficient Vitamin D3 states have not been proven to pose significant acute threats in otherwise healthy individuals. However, inadequate circulating Vitamin D3 stores may be potentially detrimental during periods of critical illness, infection or injury due the effect of bioactive Vitamin D3 on the immune system. These situations represent conditions where the inflammatory state is heightened and the injured patient is at greatest risk.

Nevertheless, the impact of inadequate circulating levels of Vitamin D3 on survival and clinical outcome in severely injured and/or critically-ill trauma patients after seemingly minor injury has not been firmly established and thus, it remains poorly characterized. The purpose of this study was to assess the effect of Vitamin D3 status in trauma patients sustaining critical injury requiring ICU admission on in-hospital mortality. As traumatic injury is not a planned event, we also sought to define the prevalence of Vitamin D3 insufficiency in this cohort of critically injured trauma patients requiring admission to the SICU.

Materials and Methods

We conducted a prospective observational study of critically injured trauma patients requiring admission to the surgical ICU at an urban level I trauma center from September 2009 through February 2012. We identified 434 trauma patients that met inclusion criteria for the study, which included all injuries requiring management in the ICU for > 24 hours and the availability of a baseline Vitamin D3 level within 72 hours of ICU admission directly from the emergency department (ED) or operating room (OR) after acute trauma. Exclu-

sion criteria were no expectation of survival due to severe, traumatic brain injury and lack of a baseline measurement of serum Vitamin D3 level. The research protocol was approved by the Morehouse School of Medicine Institutional Review Board and the Grady Research Outcomes Committee.

We used a previously validated Vitamin D3 deficiency scale to define Vitamin D3 insufficiency as 14 to 26 ng/mL, severe insufficiency as < 14 ng/mL and sufficiency as ≥ 27 ng/ml.

Vitamin Severity Scale	Lower Limit	Upper limit	% Distribution
Deficient	4 ng/ml	≤ 13 ng/ml	39.4%
Insufficient	14 ng/ml	26 ng/ml	47.93%
Sufficient	≥ 24 ng/ml	≤ 100 ng/ml	12.67%

Table 1: *Vitamin D Severity Scale.*

The majority of critically injured trauma patients (87.3%) had inadequate circulating vitamin D3 stores at baseline upon admission to the intensive care unit.

Characteristics	Frequency (n)	Percentage (%)
Male	332	76.5
Female	102	23.5
African- American	227	52.3
Caucasian	157	36.2
Blunt	358	82.5
Penetrating	76	17.5
Pneumonia	85	19.4
Respiratory Failure	146	33.6
Deaths	30	6.91

Table 2: *Baseline Population Characteristics (N = 434).*

Baseline characteristics of trauma patients admitted to our surgical ICU revealed that the majority of patients were male, 82% Had blunt trauma and over 52% were African- American. The overall mortality rate was 69.1%. Over 33% had acute respiratory failure at the time of admission and 19.4% developed Pneumonia.

We examined baseline patient demographics and characteristics, including age, gender, and race, injury severity scores (ISS), and nutritional and metabolic parameters, such as pre albumin, albumin, and serum calcium levels. The primary outcome assessed was in-hospital mortality. The secondary measure was Vitamin D3 status in our trauma patient cohort.

The 25-hydroxy-Vitamin D3 levels were measured using high-pressure liquid chromatography and tandem mass spectrometry (Quest Diagnostics Lab, Valencia, CA). Serum Vitamin D3 values were not immediately available to guide therapy for 10 to 14 days as this laboratory analysis was sent out for processing. Follow up Vitamin D3 levels were not routinely drawn or measured in this study as research suggest it takes up to 3 months of replacement therapy to reach steady-state concentrations based on currently recommended management strategies. We therefore routinely supplement at-risk trauma patients with suspected Vitamin D3 insufficiency with cholecalciferol along with other indicated nutritional supplementation as needed as a matter of ICU management. All patients were treated in a similar fashion with the institution of empiric Vitamin D3 replacement therapy- cholecalciferol at a dose of 50,000 IU/week according to recommendations by Holick [11] after enteral assess and nutritional support were established, which was typically within > 48 hours of ICU stay.

One-way Analysis of Variance (ANOVA), Student-t and Fisher Exact tests were used to evaluate continuous variables and chi-square was used to assess discrete variables. The data was summarized as mean values ± standard deviation. A p-value of < 0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS 17.0 software (Chicago, IL).

Results and Discussion

The mean age for the sufficient group was 9 years higher than those with severe vitamin D insufficiency and 5 years older than those in the Vitamin D insufficient group. The mean Vitamin D levels for the sufficient group was 3.8x higher than for the severely insufficient group and 1.8x higher than the insufficient cohort. The mean ISS was 15.29 ± 7.16, which was not significantly different between groups. The ICU length of stay (LOS) was over 2.6 days longer in the severely insufficient group (11.23 days) versus the Vitamin D insufficient (8.60 days) and sufficient (8.27 days) groups (p = 0.234). There was no significant difference in serum calcium, albumin and pre albumin levels.

Variable	Total Vitamin D Group (N =434) (mean ± SD)	Severe Vitamin D Insufficiency (N =171) (mean ± SD) ≤14 ng/ml	Moderate Vitamin D Insufficiency (N=208) (mean ± SD) 15 to 28 ng/ml	Vitamin D Sufficiency (N=55) (mean ± SD) ≥29 ng/ml	p value
Vitamin D level (ng/ml)	17.0 ± 9.20	8.98 ± 2.74	18.82 ± 3.64	34.38 ± 8.82	<0.001
Vitamin D severity distribution (%)	100%	39.4%	47.93%	12.67%	<0.001
Injury Severity Score(ISS)	15.29 ± 7.16	15.18 ± 6.66	15.64 ± 6.42	14.32 ± 8.97	0.386
Length of ICU Stay (days)	9.20 ± 14.49	11.23 ± 16.35	8.60 ± 14.22	8.27 ± 12.93	0.234
Age (years)	42.48 ± 17.96	39.55 ± 16.71	43.32 ± 17.87	48.2 ± 20.43	0.011
Deaths, N	30(6.91%)	12(7.02%)	16(7.69%)	2(3.64%)	0.0158
Serum Calcium	8.71 ± 0.76	8.63 ± 0.83	8.74 ± 0.69	8.94 ± 0.82	0.3427
Albumin	3.58 ± 1.83	3.42 ± 0.75	3.69 ± 2.52	3.60 ± 0.60	0.901
Pre albumin	18.39 ± 6.84	16.94 ± 7.25	19.40 ± 6.36	18.68 ± 6.36	0.7389

Table 3a: *Characteristics groups based on Vitamin D Severity.*

One-way Analysis of variance revealed the sufficient Vitamin D group was different from the insufficient and deficient groups. There was no difference in the injury severity. Mortality was higher in the groups with Vitamin D stores. There was difference in ICU length of stay. A p value < 0.005 was deemed significant.

However, in a multivariate-way post-hoc analysis, pre albumin was found to be statistically higher and different that both the Vitamin D3 deficient and sufficient cohorts. There was no difference in the injury severity score (ISS) or ICU length of stay (LOS) among groups.

Characteristics (Post-hoc)		Severe Vitamin D Insufficiency ≤ 13 ng/ml or (95% CI)	Moderate Vitamin D Insufficiency 14 to 26 ng/ml or (95% CI)	Vitamin D Sufficiency ≥ 27ng/ ml or (95% CI)
Injury Severity Score (ISS)	Low ISS ≤ 15	1.00	1.00	1.00
	High ISS > 15	0.956 (0.62 - 1.44)	1.18 (0.78 - 1.79)	0.74 (0.38 - 1.45)
Age, Years	14 - 65	1.00	1.00	1.00
	68 - 92	0.52 (0.26 - 1.4)	1.35 (0.70 - 2.58)	1.95 (0.86 - 4.66)
Length of ICU Stay	≤ 30Days	1.00	1.00	1.00
	30 +	1.86 (0.84 - 4.10)	0.62 (0.28 - 1.40)	0.60 (0.13 - 2.72)
Serum Calcium	Low Calcium	1.00	1.00	1.00
	Normal Calcium	0.90 (0.57 - 1.43)	1.07 (0.68 - 1.70)	1.10 (0.51 - 2.39)
Albumin	Low Albumin	1.00	1.00	1.00
	Normal Albumin	0.62 (0.36 - 1.07)	1.34 (0.77 - 2.33)	1.77 (0.66 - 4.77)
Prealbumin	Low Prealbumin	1.00	1.00	1.00
	Normal Prealbumin	0.75 (0.47 - 1.20)	1.63 (1.02 - 2.61)	0.60 (0.29 - 122)

Table 3b: *Multi variate analysis of group based on Vitamin D severity.*

Post-hoc one-way analysis of variance revealed a statistically signicant difference in Prealbumin level in the moderately insufficient Vitamin D group compared to both the sufficient and deficient groups. There was no difference in the injury severity and ICU length of stay. P value < 0.005 was deemed significant.

Out of the 434 patients that were evaluated, 39.4% had severe insufficiency (< 14 ng/ml), 47.9% (208) of patients had Vitamin D insufficiency (14 - 26 ng/mL), and 12.7% (55 patients) had sufficient (≥ 27 ng/mL) baseline Vitamin D levels.

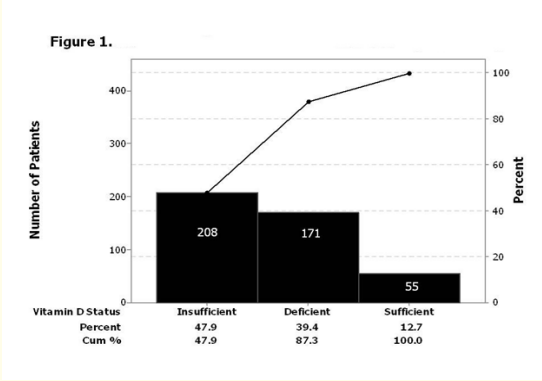

Figure 1: *Baseline Vitamin D levels.*

Consequently, 87.3% (379) of the patients had Vitamin D insufficiency (≤ 26 ng/ml) upon admission to the SICU. The majority (332) of patients were males (76.5%) compared to 102 women (23.5%). There were 229 African-American (52.6%) patients, 155 were Caucasian patients (35.8%), and 39 patients (9%) were Hispanic. The preponderance of patients (82.5%) suffered from blunt trauma and the remainder (17.2%) sustained penetrating injuries. The overall mortality rate for the total group was 6.91%. Over 33% of patients had acute respiratory failure at the time of admission and 19.4% developed pneumonia.

The mortality rate was 7.69% in the insufficient group and 7.02% in the severely insufficient group; the crude mortality rate was 7.39% (28/379) in the overall insufficient group versus 3.64% (2/55) in the sufficient group (p = 0.0158), which equated to a 2-fold higher mortality rate for the insufficient group.

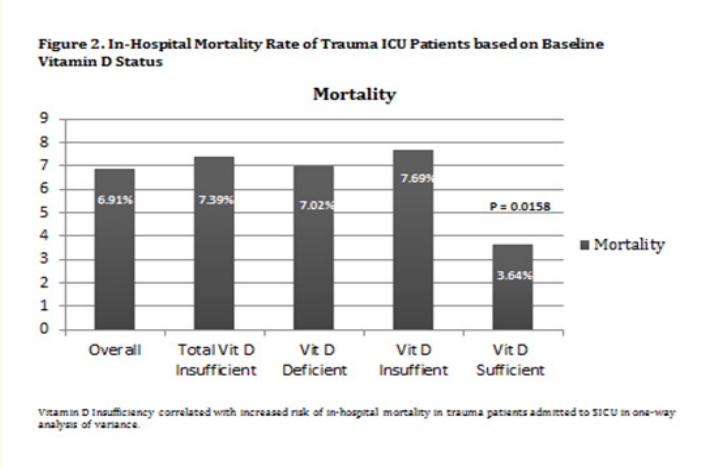

Figure 2: *In Hospital mortality rate of Trauma ICU patients based on Baseline Vitamin D Status.*

As discussed previously, several investigators have shown increased risk for mortality and complications in mixed populations of surgical critical care patients [3,5,6,7]. Nevertheless, the adverse effect of inadequate Vitamin D3 levels specifically on the outcomes of severely injured and/or critically ill trauma patients requiring admission to the surgical ICU (SICU) has not been clearly elucidated. Consequently, scant evidence guides clinicians in the management of severely injured trauma patients with Vitamin D3 deficiency in the setting of critical illness in the ICU. Vitamin D3 deficiency has become a commonly recognized condition in critically ill hospitalized patients [3-10]. In fact, it has been suggested that inadequate Vitamin D3 states are prevalent in the SICU and was found to be present in over 90% of a mixed cohort of ICU patients in one study [3]. Similarly, in another study of 134 medical ICU patients, 79% (106) of patients were noted to have insufficient serum Vitamin D levels [4]. In a similar manner, the majority of our critically injured trauma patients (87.3%) were found to have inadequate serum Vitamin D3 levels upon admission to the ICU. In a like fashion, low Vitamin D3 levels have been demonstrated by other investigators to be common among patients admitted to the ICU and associated with increased risk for poorer outcomes [4,5,6,8,9]. These data support the theory that a sufficient Vitamin D3 concentration may provide a potential survival advantage for trauma patients after severe injury requiring management in the SICU [9,11,14,22].

Just as Vitamin D3 deficiency has been shown to be associated with increased risk of mortality in the general population [2,12], Vitamin D3 insufficiency has been shown to be associated with greater risk of poor outcomes, including increased risk of mortality, in both critically ill ICU patients [3-10]. However, a direct correlation with worse outcome specifically in subsets of severely injured and/or critically ill trauma patients in the ICU setting has not been clearly established. Out of the 30 trauma patients that died before hospital discharge in our cohort, 93.3% of these individuals had insufficient Vitamin D levels at baseline after ICU admission and initiation of critical care management. The overall mortality rate (7.39% versus 3.64%) in the patients with insufficient circulating Vitamin D3 levels was greater than 2 times higher than in those with sufficient initial serum 25-hydroxvitamin D3 concentrations in our cohort.

Historically, Vitamin D3 levels less than 5 to 7 ng/mL have been thought to only lead to Vitamin D3 deficiency related manifestations, such as rickets with resultant osteomalacia and pathologic fractures, and serum levels of 20 ng/mL or greater were considered to be normal [23-26]. In fact, previous Institute of Medicine (IOM) guidelines targeted a vitamin D3 level of ≥ 20 ng/mL for good bone and general health for the majority of individuals [27,28].

However, mounting clinical and basic scientific data suggest higher levels may be more desirable and needed to facilitate optimal immunologic protection and improve overall health [3,5,11,29,30]. Actually, a distinguished group Vitamin D3 experts at a past international consensus conference suggested a minimum serum Vitamin D3 level should be between 20 and 30 ng/mL may be more desirable, which supports our target level of 27 ng/mL or greater as theoretically sufficient, and/or representing only a minimally deficient state [3,31,32]. Based on the multiple Vitamin D3 study group and expert panel recommendations, various definitions of Vitamin D3 insufficiency persist in the literature. Consequently, the prevalence of Vitamin D3 inadequacy in our patient cohort would have ranged from 71.5% and 97.7% depending on the parameters used [3,4,5,9,11,14,15,30,31].

Vitamin D Deficiency level	N	Total Population (%)	Mortality Rate (%) [N of Deaths]
Vitamin D ≤ 20 ng/mL*	311	71.5	7.40% [23]
Vitamin D ≤ 24 ng/mL¥	366	84.1	7.65% [28]
Vitamin D ≤ 30 ng/mL	379	87.3	7.39% [28]
Vitamin D ≤ 32 ng/mL¶	406	93.3	7.14% [29]
Vitamin D ≤ 36 ng/mL	412	95.4	7.04% [29]
Vitamin D < 40 ng/mL	425	97.7	7.06% [30]

Table 4: *Comparison of Vitamin D deficiency in Trauma Patients in Intensive Care Unit.*

Prevalence of Vitamin D deficiency in our cohort based on prior definitions of Vitamin D deficiency varied from 71.5% to 97.7% and crude mortality rate from 7.04% to 7.65%.

It has been shown that bioactive Vitamin D3 is a powerful modulator of the immune response [32-36]. In fact, it is without question one of the major regulatory hormones of the entire immune system [20,23]. Therefore, it is plausible that the insufficient Vitamin D3 state in the setting of critical illness after severe trauma may be associated with an increased risk of invasive infection, SIRS, severe sepsis and sepsis related complications as occurs in at risk trauma patients [20,21,37]. Sufficient Vitamin D3 levels have been shown to augment the innate immune response and jump start the host defense system via induction of the release of endogenous antimicrobial peptides (EAP), such as beta-defensins and cathelicidin (LL-37) [34,35,36,38,39]. On the other hand, it helps to turn off the humoral and cell-mediated immune responses during states of Vitamin D adequacy, which is typically above 30 ng/mL [40]. This could have theoretically contributed to the decreased mortality rate observed in the cohort with adequate baseline vitamin D3 levels by abating the septic response.

Consequently, our critically injured or ill trauma patients with a higher baseline 25-hydroxy-Vitamin D3 levels may have had a greater degree of immunologic protection and ability to recover from additional inflammatory insults and acquired infections than in the insufficient group. These findings are also supported by the fact that almost all of the patients that died (93.3%) had a Vitamin D level ≤ 28 ng/mL and were in the insufficient or severely insufficient Vitamin D category. Thus, it is not unreasonable to suspect that severely injured trauma patients with inadequate levels of circulation Vitamin D3 may be less able to mount a complete immune response to infectious or physiologic insult in the setting of critical illness. This could have led to a more pronounced and/or prolonged inflammatory response, which would potentially have worsened their clinical outcome by decreasing their immunologic barriers and susceptibility to invasive infection and severe sepsis.

These observations may partially explain the 2-fold higher mortality rate noted in patients with Vitamin D3 inadequacy. Available research suggests that patients with low serum Vitamin D enter into a vicious cycle of hypovitaminosis-D3, increased inflammatory milieu, and acute organ impairment due to immunologic injury, such as acute kidney injury, acute lung injury or acute respiratory distress

syndrome and even stroke [16,17,18,40,41,42,43,44]. These may or may not resolve effectively by simple Vitamin D3 supplementation after the insult(s) has occurred as other contributory factors or physiologic abnormalities may exist; however, further research needs to be conducted to answer this all important question.

Vigilance is still needed to identify subclinical hypovitaminosis-D3 in this high risk patient population and early supplementation with cholecalciferol (Vitamin D3) should be considered [3]. Nevertheless, pre-morbid and pre-injury nutritional optimization via Vitamin D3 supplementation may offer the best chance to improve outcomes after severe, traumatic injury and other unplanned critical illness requiring admission and management in the intensive care unit setting, which may help to reduce in-hospital mortality [3,44].

Conclusion

In summary, Vitamin D3 insufficiency and deficiency may explain some of the excess and unexpected mortality experienced in critically injured trauma patients who are admitted to the SICU. The association between low Vitamin D3 levels and other common conditions, such as SIRS, septicemia, malnutrition and metabolic syndrome in critically ill ICU patients has been fairly well established. Based on our study findings, Vitamin D3 insufficiency as defined by a serum Vitamin D3 level of ≤ 26 ng/mL may be associated with an increased risk of morbidity and mortality in critically injured trauma patients [45]. Consequently, a survival benefit from higher circulating Vitamin D3 concentrations may exist. Ongoing and more in depth study of these preliminary findings is warranted. Similar to other studies, we conclude that insufficient 25-hydroxy-Vitamin D3 levels may be an independent risk factor for worse clinical outcomes and increased risk of in-hospital death in severely injured and/or critically ill trauma patients requiring management in the ICU.

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Conflict of interest

All authors declare that they have no financial interest as it relates to this manuscript or have any conflicts of interest.

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