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ORIGINAL RESEARCH

Preoperative Correction of Low Hemoglobin Levels Can Reduce 1-Year All-Cause Mortality in Osteoporotic Hip Fracture Patients: A Retrospective Observational Study

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Purpose: Osteoporotic hip fracture surgery is associated with a risk of morbidity and mortality. Admission hemoglobin levels <10 g/dL have been documented as a strong predictor of mortality risk. This study aimed to investigate the mortality outcome between osteoporotic hip fracture patients who had preoperative hemoglobin levels raised to ≥10 g/dL and those with hemoglobin levels were <10 g/dL.

Patients and Methods: This 5-year retrospective observational study included 226 participants with osteoporotic hip fractures that required surgery and who had admission hemoglobin levels <10 g/dL. Patients were categorized into two groups: those with corrected preoperative hemoglobin ≥10 g/dL and those with either corrected or uncorrected preoperative hemoglobin <10 g/dL. Outcomes were analyzed using Cox proportional hazard regression adjusted for confounders. Results are presented as hazard ratio (HR) and 95% confidence interval (95% CI).

Results: Among 226 the patients, the overall mortality rate was 17.25% (n=39/226) of the 226 patients, 93 (41.15%) had their hemoglobin levels raised to ≥10 g/dL by red blood cell transfusion. Multivariable analysis after adjustment for confounders showed a 50% lower incidence of mortality among patients with preoperative hemoglobin levels ≥10 g/dL than among those with hemoglobin levels <10 g/dL (HR 0.50, 95% CI (0.25–0.99), p=0.048).

Conclusion: In osteoporotic hip fracture patients with admission hemoglobin <10g/dL, raising preoperative hemoglobin levels to ≥10 g/dL can significantly reduce the risk of mortality. Testing for and correction of low preoperative hemoglobin levels is of value in hip surgery patients.

Keywords: osteoporosis, hip fracture, anemia, mortality

Introduction

Hip fracture is a major public health concern as it is associated with an increased risk of morbidity, mortality, loss of independence and a high healthcare burden.[1] A wide variation in hip fracture incidence has been reported globally. An increase in the incidence of hip fracture from 1.26 million in 1990 to 4.5 million by 2050 has been predicted.[2] The first-year post-hip fracture mortality rate in the elderly is high, ranging from 18% to 30%.[3–5] The risk of death increases approximately 4% per year in elderly patients. The most critical period is the first year following the fracture event.[6] After 2 years, the risk of death was found to decrease noticeably but the risk was still significantly greater than in the control groups with no hip fracture.[7]

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Predictive factors found to be related to an increased mortality rate in osteoporotic hip fracture patients include male gender, advanced age, ethnicity, physical performance, institutionalization, type of fracture, operative treatment method, longer time from injury to operation, results of some biochemical investigations and underlying medical illness.[8–12] One of the most frequently reported predictive factors was low hemoglobin levels. Among geriatric hip fracture patients, approximately 40% present with hemoglobin levels less than 12 g/dL.[13] In addition, admission hemoglobin levels in the anemic range (<10 g/dL) have been reported to be a strong predictor of increased mortality risk following hip fracture.[10,14] In addition to an increased in mortality rate, anemia in hip fracture patients has been reported to be related to increased transfusion rates, hospital re-admission and poorer functional outcomes regardless of the severity of the anemia.[15,16] Tests for hemoglobin levels prior to hip fracture surgery are widely available, easy to interpret and inexpensive. Importantly, low hemoglobin levels are modifiable predictors of mortality and can be corrected by red blood cell transfusion. Currently, evidence regarding the timing of hemoglobin correction by transfusion, ie, before, during or after hip fracture surgery, still needs to be clarified. Most studies have focused on the benefits of correction during the intra- and postoperative periods.[17,18] There are as yet no studies of mortality rates in osteoporotic hip fracture patients with admission hemoglobin levels <10 g/dL who had been transfused preoperatively to raise their hemoglobin to ≥10 g/dL. The present study aimed to determine the 1-year all-cause mortality outcomes in osteoporotic hip fracture patients who had preoperative hemoglobin levels <10 g/dL and who had had preoperative transfusions to raise their hemoglobin to ≥10 g/dL.

Patients and Methods

A 5-year retrospective observational study was conducted between January 2014-December 2018 in tertiary care medical Center in Thailand. The study was approved by local ethical committee of the Faculty of Medicine, Chiang Mai University. The patients' Clinical and biochemical data were retrieved from the electronic medical records. The inclusion criteria were 1) Thai patients age above 50 years with osteoporotic hip fracture resulting from simple fall, 2) patients who had subsequently undergone any type of hip fracture operation and 3) admission hemoglobin levels <10 g/dL. The exclusion criteria were mentioned in our previous publication.[10] In brief, patients with bilateral hip fracture, previous hip fracture, more than one area of fractures, pathological hip fractures or high energy mechanism fractures were excluded. Data retrieved included basic demographics, underlying medical illness, type of fracture, type of surgery, American Association of Anesthesiologist (ASA) score[19] and time to operation. Biochemical investigation information included admission hemoglobin levels, post-transfusion hemoglobin levels, creatinine with estimated glomerular filtration rate (eGFR) and serum albumin levels. The 1-year all-cause mortality data was acquired from medical records for in-hospital mortality and from the Thailand Civil Registration office in cases where data was not available in hospital records. The time to death started at the date of hip injury. eGFR was calculated using the Modification of Diet in Renal Disease Study (MDRD) formula. The admission hemoglobin level was defined as the level on the first day of admission. The preoperative hemoglobin level was defined as the level, either the corrected or uncorrected, obtained prior surgery. For patients whose level was not corrected by transfusion, admission hemoglobin levels were considered to be equivalent to preoperative levels.

The decision whether to transfuse red blood cells or not was made by each individual surgical team. The acceptable threshold level for hemoglobin before proceeding to surgery was determined by the individual surgeons. For this study, patients were categorized into one of two groups: those with corrected preoperative hemoglobin ≥10 g/dL and those with corrected or uncorrected preoperative hemoglobin <10 g/dL. All patients with preoperative hemoglobin ≥10 g/dL had been transfused with red blood cells. All methods were performed in accordance with the relevant guidelines and regulations. Informed consent was not obtained due to retrospective nature of the study.

Statistical Analysis

Statistical analysis was conducted using STATA program version 15.0. Categorical data are presented as counts and percentages. Continuous variables are presented as means and standard deviations (SD). For inferential statistics, Fisher's exact test was used for categorical variables and Student's *t*-test for continuous variables. Univariable and multivariable analyses were performed using Cox proportional hazard regression between mortality and predictors and hazard ratio

(HR) with a 95% confidence interval (95% CI). In the multivariable analysis, potential confounders, including age, sex, ASA score, dementia and location of fracture, were adjusted. Time from injury to time of operation ≥48 hours was adjusted by stratified random sample method. Multiple imputation analysis was employed for predictive variables with more than 5% missing. Statistical significance was set as $p < 0.05$. The collinearity of each potential confounder was evaluated. Potential confounders which had a variance inflation factor (VIF) value >5 were excluded from the multivariable analysis. Subgroup analysis comparing patients that had corrected hemoglobin levels ≥10 g/dL and patients with corrected hemoglobin levels < 10g/dL was planned to demonstrate. Sample size was calculated by means of an exponential test comparing two independent hazard rates. Adequate sample size was demonstrated if the backward calculation of power of analysis was more than 0.80.

Results

There were 226 patients who had osteoporotic hip fracture with admission hemoglobin levels <10 g/dL. The overall mortality rate was 17.25% (n=39/226). There were 93 patients (41.15%) that had corrected hemoglobin levels ≥10 g/dL and 133 patients (58.84%) with corrected or uncorrected hemoglobin levels <10g/dL. Leukocyte poor packed red blood cells transfusion was used in all patients who received the blood transfusion. The majority of the patients were female (74.34%, n=168/226). The mean age was 81.51±8.28 years. Mean body mass index (BMI) was 20.06±3.74 kg/m^2. The most common underlying comorbidity was hypertension (65.93%, n=149/226) followed by diabetes mellitus (23.89%, n=54/226). Intertrochanteric fracture was the most common type of injury (78.32%, n=177/226). Cephalomedullary nailing was the most frequently performed operation (56.19%). Most patients had time from injury to operation ≥48 hours (98.67%, n=223/226). BMI was significantly higher in patients with preoperative hemoglobin <10 g/dL than those with ≥10 g/dL ($p = 0.044$). Other Clinical factors were not significantly different between the two groups. As to admission biochemical data, all laboratory tests, including admission hemoglobin levels, were similar between the groups although preoperative hemoglobin levels were significantly higher in the group which received red blood cell transfusion ($p < 0.001$) (Table 1). In patients who had preoperative hemoglobin <10 g/dL (n = 133), 94 patients (70.68%, n=94/133) received the preoperative transfusion.

Univariable analysis revealed that the patients whose hemoglobin had been increased to ≥10 g/dL showed no significant reduction in mortality rate compared to patients whose hemoglobin remained <10 g/dL. All confounders had a variance inflation factor (VIF) value <5. We did not perform multiple imputation analysis because there was no missing data more than 5% in potential confounders. After multivariable analysis and adjusting for potential confounders including male, age at admission ≥85 years, dementia, ASA score >2, fractured neck of femur, time from injury to operation ≥48 hours, a significant reduction in mortality rate of 50% was observed (HR 0.50, 95% CI (0.25–0.99) and $p = 0.048$) (Table 2). The survival graph comparing survival probability between patients who had preoperative hemoglobin ≥10 g/dL and patients who had preoperative hemoglobin <10 g/dL after adjusting the confounders is shown in Figure 1. Univariable and multivariable analysis of 1-year all-cause mortality in subgroup analysis comparing 93 patients that had corrected hemoglobin levels ≥10 g/dL and 94 patients with corrected hemoglobin levels <10g/dL. Stratified by time from injury to operation ≥48 hours or <48 hours showed a strongly significant reduction in 1-year mortality of 41% in patients had corrected hemoglobin levels ≥10 g/dL compared to patients with corrected hemoglobin levels <10g/dL. After adjusting the confounders (HR 0.41, 95% CI (0.20–0.82) and p=0.013) (Table 3).

Discussion

The singular finding in this study was that an increase of preoperative hemoglobin levels to ≥10 g/dL had an association with a 50% reduction in 1-year mortality among the osteoporotic hip fracture patients. The results from subgroup analysis comparing 1-year mortality between patients had corrected hemoglobin levels ≥10 g/dL and patients with corrected hemoglobin levels <10g/dL was also confirmed our finding. This is an indication that preoperative hemoglobin level is an important and modifiable factor in osteoporotic hip fracture patients who will be undergoing surgery.

Preoperative anemia has been reported to be associated with an increased risk of morbidity and mortality in osteoporotic hip fracture patients, particularly those with hemoglobin <10 g/dL.[10,14] The anemia can be the result of trauma-induced blood loss, iron deficiency, anemia from chronic comorbidities or, in the elderly, bone marrow

Table 1 Baseline Clinical and Biochemical Characteristics of Hip Fracture Patients (n=226)

Characteristics	Preoperative Hemoglobin ≥ 10 g/dL (n=93)	Preoperative Hemoglobin <10 g/dL (n=133)	*p*-value
Clinical factors			
Male, n (%)	20 (34.5)	38 (65.5)	0.279
Age (years), Mean±SD	81.23±8.45	81.71±8.18	0.663
BMI at admission (kg/m^2), Mean±SD (n=225)	19.45±3.31	20.47±3.97	0.044
Underlying diseases, n (%)			
Dementia	5 (41.7)	7 (58.3)	1.000
Malignancy	0 (20)	5 (100)	0.079
Hypertension	64 (23.0)	85 (57.0)	0.478
History of myocardial infraction	0 (20)	5 (100)	0.079
Congestive heart failure	0 (0)	1 (100)	1.000
Chronic obstructive pulmonary disorder	5 (29.4)	12 (70.6)	0.019
Diabetes mellitus	23 (42.6)	31 (57.4)	0.874
Rheumatologic disease	16 (45.7)	19 (54.3)	0.579
Cerebrovascular disease	13 (59.0)	9 (41.0)	0.109
ASA score >2, n (%)	44 (23.6)	57 (56.4)	0.587
Type of fracture, n (%) Fractured neck of femur Intertrochanteric fracture	 19 (38.8) 74 (41.8)	 30 (61.2) 103 (58.2)	0.745
Surgery type, n (%)			0.271
Dynamic hip screw	25 (55.6)	20 (44.4)	
Cephalomedullary nailing	47 (37.0)	80 (63.0)	
Stable angle plating	2 (40.9)	3 (60.0)	
Multiple screw fixation	1 (33.3)	2 (66.7)	
Arthroplasty	18 (39.1)	20 (60.9)	
Time from injury to operation ≥48 hours, n (%)	93 (41.7)	130 (58.3)	0.270
Biochemical factors			
Admission hemoglobin levels (g/dL), Mean±SD	8.78 (0.91)	8.68 (1.07)	0.473
Preoperative hemoglobin levels (g/dL), Mean±SD	10.79 (0.74)	9.17 (0.78)	<0.001
Admission estimated glomerular filtration rate (mL/min/1.73m^2), Mean±SD	53.77 (26.59)	48.69 (28.26)	0.175
Admission serum albumin level (g/dL), Mean±SD (n=45)	3.21 (0.40)	3.25 (0.57)	0.809

Abbreviations: SD, standard deviation; BMI, body mass index; ASA score, American Society of Anesthesiologists (ASA) Physical Status Classification.

Table 2 Univariable and Multivariable Analysis of 1-Year All-Cause Mortality in Hip Fracture Patients Stratified by Time from Injury to Operation ≥48 Hours or <48 Hours

Characteristics	Univariable Analysis			Multivariable Analysis		
	Hazard Ratio	95% Confidence Interval	*P*-value	Hazard Ratio	95% Confidence Interval	*P*-value
Preoperative Hb >10 g/dL	0.57	0.29–1.12	0.102	0.50	0.25–0.99	0.048
Male*	1.60	0.82–3.11	0.168	1.40	0.72–2.74	0.318
Age at admission ≥85 years*	1.42	0.76–2.68	0.275	1.38	0.72–2.63	0.328
Dementia*	2.47	0.88–6.97	0.087	2.94	1.02–8.46	0.045
ASA score >2*	2.83	1.45–5.50	0.002	3.04	1.55–5.99	0.001
Fractured neck of femur*	0.74	0.33–1.68	0.474	0.89	0.38–2.04	0.775

Note: *Confounders.
Abbreviations: Hb, hemoglobin; ASA score, American Society of Anesthesiologists (ASA) Physical Status Classification.

dysfunction. However, there is currently no standard recommendation regarding who should have anemia correction by transfusion before hip fracture surgery, when such a transfusion should be administered and there is no standard cutoff values used to define the preoperative anemia.[20] There has been a wide variability in studies about the timing of transfusion in hip fracture surgery, ie, whether it should be preoperative, intraoperative, or postoperative. Most studies which included a large sample explored the outcomes of postoperative transfusion.[18,21] However, the benefits of preoperative optimization of hemoglobin levels have been established for other types of orthopaedic surgeries including hip arthroplasty and total knee arthroplasty. Observed benefits have included a decrease in complications, readmission, postoperative transfusion and length of hospital stay.[22,23]

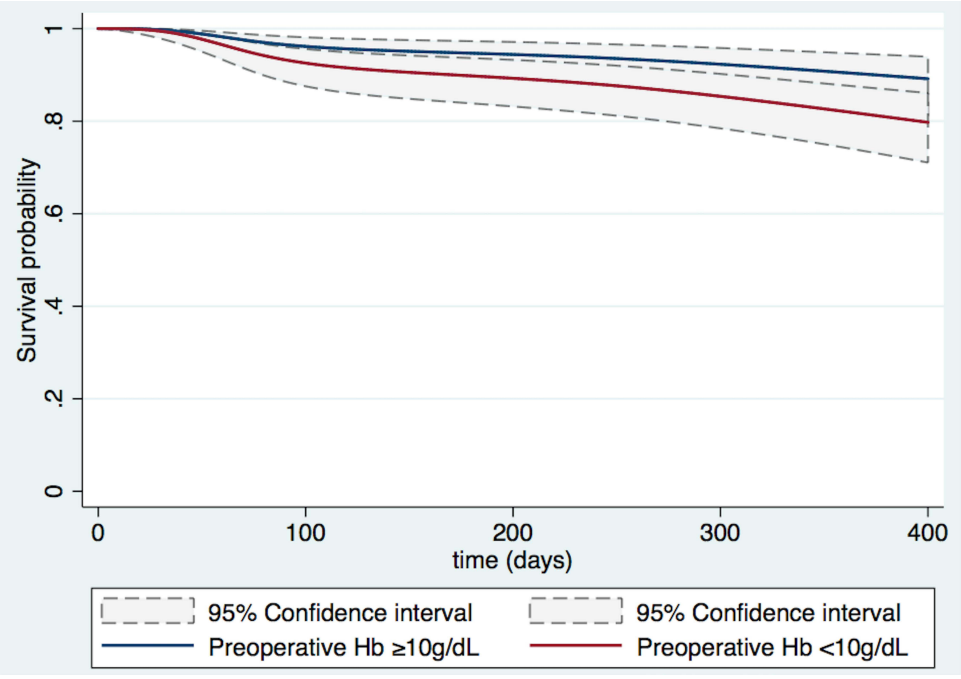

Figure 1 The survival graph comparing survival probability between patients who had preoperative hemoglobin ≥10g/dL and patients who had preoperative hemoglobin <10g/dL after adjusting male, age at admission ≥85 years, dementia, ASA score >2, fractured neck of femur and time from injury to operation ≥48 hours.
Abbreviation: Hb, hemoglobin.

Table 3 Univariable and Multivariable Analysis of 1-Year All-Cause Mortality Comparing 93 Patients That Had Corrected Hemoglobin Levels ≥10 g/dL and 94 Patients with Corrected Hemoglobin Levels <10g/dL. Stratified by Time from Injury to Operation ≥48 Hours or <48 Hours (Subgroup Analysis)

Characteristics	Univariable Analysis			Multivariable Analysis		
	Hazard Ratio	95% Confidence Interval	*P*-value	Hazard Ratio	95% Confidence Interval	*P*-value
Preoperative Hb >10 g/dL	0.46	0.23–0.93	0.029	0.41	0.20–0.82	0.013
Male*	1.54	0.76–3.09	0.228	1.22	0.60–2.74	0.575
Age at admission ≥85 years*	1.46	0.75–2.83	0.267	1.43	0.73–2.82	0.297
Dementia*	1.83	0.56–6.01	0.314	2.23	0.67–7.43	0.193
ASA score >2*	3.38	1.62–7.04	0.001	3.67	1.74–7.72	0.001
Fractured neck of femur*	0.69	0.28–1.65	0.400	0.80	0.33–1.96	0.632

Note: *Confounders.
Abbreviations: Hb, hemoglobin; ASA score, American Society of Anesthesiologists (ASA) Physical Status Classification.

The present study found that preoperative transfusion which raised hemoglobin to ≥10 g/dL was significantly associated with a 50% reduction in 1-year all-cause mortality. We proposed that red blood cell transfusion can facilitate an increase in the oxygen-carrying capacity of blood and that it promotes positive outcomes hip fracture surgery in multiple ways. First, a preoperatively corrected hemoglobin level can also raise the postoperative level. A study revealed that an adequate postoperative hemoglobin concentration was linked to better short-term functional recovery after hip fracture surgery[24] and a reduction in symptoms of anemia, eg, fatigue, weakness and decreased physical function. Treadmill testing in a healthy population showed that reduction in VO2 max (maximum oxygen consumption) had a positive correlation with a reduction in hemoglobin levels.[25] Similarly, there was an improvement in aerobic exercise capacity in patients with end-stage renal disease who had had their hemoglobin levels raised by erythropoietin injection.[26] Lower functional capacity and physical fitness have been reported to be related to increased mortality risk, especially in the elderly.[27] Second, a prior study demonstrated that liberal transfusion aimed at achieving hemoglobin levels of 10 g/dL (liberal strategy) showed a reduction in the rate of major cardiac events twice that with a hemoglobin target at 8 g/dL (restrictive strategy).[28] In addition, patients with postoperative anemia demonstrated a higher incidence of delirium and nosocomial infection.[29,30] Both prolonged delirium or cognitive impairment and nosocomial infection were associated with an increased risk of death.[31] However, the present study did not include details of the causes of death.

Nevertheless, a red blood cell transfusion itself can increase morbidity in hip fracture surgery patients, with most deaths occurring during the postoperative period. An increased rate of urinary tract infection following major orthopedic surgery has also been reported.[32] Other adverse events that can occur after perioperative transfusion include transfusion-associated circulatory overload, hemolytic reactions, allergic reactions, transfusion-related infection and transfusion-related lung injury.[33,34] Storage of red blood cell for more than 2 weeks has been found to be related to a high risk of in-hospital mortality and postoperative complications.[35] Therefore, a trade-off must be made between the risk of the negative effect of preoperative anemia and the potential adverse effects of blood transfusion.

We acknowledge some limitations in this study. As this is a retrospective study, some selection bias may have been introduced. Future studies using a randomized controlled trial are warranted to more clearly demonstrate actual benefits. Some data such as reason for transfusion or total number of red blood cell transfusion did not be recorded in all patients. The preoperative volume of crystalloid administered following red blood cell transfusion was not evaluated. An excess of crystalloid fluid could result in the dilution of the hemoglobin concentration preoperatively. There was no standard guideline of when to transfuse. The decision whether to transfuse red blood cells or not was made by each individual surgical team and the acceptable threshold of hemoglobin level was decided by the individual surgeons. Data on

hemoglobin levels postoperatively and before discharge were not available in our study. In our study, the advantages of raising hemoglobin levels were postulated based on postoperative period hemoglobin levels. Thus, it was not possible to directly evaluate the association between postoperative hemoglobin levels and mortality outcomes. Also, we did not adjust for some intraoperative and postoperative factors, eg, operative time, intraoperative blood loss, postoperative infection rate, nutritional status, functional capacity after rehabilitation intervention and fall prevention strategies in the multivariable model, factors which could potentially impact mortality outcomes due to the limitation of sample size.[36] As the majority of the patients with preoperative hemoglobin levels <10 g/dL were transfused, the factor which directly influenced the mortality outcome should be preoperative level of hemoglobin instead of red blood cell transfusion. Therefore, our study cannot demonstrate the association between preoperative transfusion and mortality outcome in hip fracture patients. Further study should be conducted to address this issue. This study had several strengths. First, the ASA scores, which assess overall health status, were recorded as a preoperative risk predictor. However, some comorbidities are not incorporated in that scoring system, eg, dementia and cognitive impairment. As these factors have been linked with increased mortality in the elderly, we have included both ASA scores and dementia as adjusted confounders in multivariable analysis to reduce the occurrence of bias. Second, multiple confounding factors that could potentially impact mortality outcome, eg, sex, extreme age, ASA score and dementia, have been adjusted for accordingly. Third, including the timing of preoperative transfusion in our study was novel: few studies have considered this issue. Fourth, time from injury to operation ≥48 hours was adjusted by stratified random sample in the multivariable analysis. This helps reduce the incidence of bias as there has been a report that a delayed time of surgery of ≥48 hours can increase the risk of death.[37] Also, the sample size in our study is adequate for drawing conclusions. We used reverse power analysis to determine the hazard ratio of preoperative Hb >10 g/dL which demonstrated an adequate power of analysis (>0.80).

Conclusion

In osteoporotic hip fracture surgery patients, preoperative correction of hemoglobin to >10 g/dL was found to be associated with a 50% reduction in mortality. Hemoglobin level testing prior to surgery is not complicated and is available in virtually all institutions. It is also one of the easiest-to-modify among the predictive mortality factors in hip fracture surgery. We suggest that the preoperative hemoglobin levels may be considered as one of the preoperative planning in osteoporotic hip fracture surgery patients. Further research with a larger sample size and a randomized trial is warranted.

Abbreviations

ASA score, American Association of Anesthesiologist score; BMI, Body mass index; CI, Confidence interval; eGFR, Estimated glomerular filtration rate; HR, Hazard ratio; MDRD, Modification of Diet in Renal Disease Study; SD, Standard deviations; VIF, variance inflation factor.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval

This study was approved by local ethical committee of the Faculty of Medicine, Chiang Mai University. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was waived due to retrospective nature of the study. Authors confirmed that the data was anonymized or maintained with confidentiality.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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All authors declared no conflicts of interest for this work.

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