ISSN: 2782-7550 (Print)
ISSN: 2782-7542 (Online)

ABMS

ANNALS OF BASIC AND MEDICAL SCIENCES

A Scientific Peer Reviewed Publication of The Faculties of Basic Medical
and Basic Clinical Sciences, Usmanu Danfodiyo University Sokoto, Nigeria

A Continuing Quest for an Acceptable Alternative Sick Cell Anaemia (SCA) Severity Scoring System in a Resource-Constrained Setting

Aliyu D Waziri, Sani Awwalu, Ismaila N Ibrahim, Ibrahim U Kusfa, Aishatu M Suleiman and Abdulaziz Hassan

Department of Haematology and Blood Transfusion, Ahmadu Bello University, Zaria.

Abstract

Background: Sick cell Anaemia (SCA) severity scoring has remained challenging. Scoring systems based on clinical and certain laboratory parameters are limited in simplicity and wide applicability. This is further worsened by dearth of exhaustive and accurate patient history. This study compared a simple, laboratory parameter-based severity scoring system to a pre-existing scoring system.

Methodology: Derivation group (n = 45) and validation group (n = 300) were enrolled during steady state. Complications, haemoglobin (Hb) concentration and white blood cell counts (WBC) were documented. Severity scores were computed for each participant based on number of complications, Hb and WBC counts using a preexisting scoring system. Proposed scoring system (PropScore) was also computed based on Hb (≤ 6 , >6 to ≤ 10 and >10 (g/dl) scored as 2, 1 and 0 respectively, and WBC (≤ 10 , >10 to ≤ 20 and >20 ($\times 10^9/L$) scored as 0, 1 and 2 respectively. The aggregate scores of ≤ 1 , 2-3 and 4 were graded as mild, moderate and severe respectively. Severity scores were treated as ordinal variables and analysed using Spearman rank correlation, Kappa analyses and Kruskal Wallis H tests.

Results: The median and interquartile range (IQR) age of the derivation group was 22 (7) years while mean and standard deviation ($\pm$ SD) of the validation was 24.6 ± 7.1 years. Among the derivation group, correlation between the pre-existing score and the PropScore was $\rho = 0.844$, $p = <0.001$ while the strength of was; Kappa value = 0.745, $p = <0.001$. The values for the validation group were $\rho = 0.601$, $p = <0.001$ and Kappa value = 0.184, $p = <0.001$.

Conclusion: There is poor agreement between the proposed scoring system and the pre-existing scoring system. However, we recommend that the impact of the proposed scoring system on quality of life as well as long-term morbidity be assessed.

Keywords: Alternative, Proposed scoring system, Severity, Sick cell anaemia.

Corresponding author:

Dr Aliyu D. Waziri
Department of Haematology and
Blood Transfusion,
Ahmadu Bello University Zaria,
Kaduna State,
Nigeria.
E-mail: aliwazeery@gmail.com
Tel: +2347030980375

Introduction

Sickle cell disease (SCD) is the most common monogenetic disorder worldwide. It results from a single gene defect affecting the beta globin chain of haemoglobin. More than half of the affected world population is found in Sub-Saharan Africa and it has been estimated that by the year 2050 more than 400,000 babies will be delivered annually in the region with sickle cell disease (1). Sick Cell Disease was therefore regarded by the World Health Organization (WHO) as a public health challenge during the World Health Assembly in 2006. It exerts psycho-social and financial burdens on patients and caregivers (2,3).

Sickle Cell Anaemia (SCA) is characterized by a complex pathophysiology and varied clinical presentations ranging from mild symptoms to severe debilitating conditions. The severe conditions may include complications such as sickle cell cerebral syndrome, retinopathy, pulmonary hypertension, acute chest syndrome, avascular necrosis and severe infection by encapsulated organisms. The onset and progression of these complications in a patient can be assessed through good history taking, physical examination and radiologic as well as laboratory investigations (4).

Several researchers have attempted to predict the severity of the disease in patients with SCA using clinical history parameters such as frequency of blood transfusion, frequency of painful episodes, history of stroke, leg ulcer and other complications. Laboratory-based tests such as total White Blood Count (WBC), Haemoglobin (Hb) level, Platelet counts, Lactate Dehydrogenase (LDH), Serum albumin, C-reactive protein and transferrin levels among others were used (5,6,7).

Hedo *et al* in a case-control study of 73 patients, studied 7 acute phase reactants and found out that serum transferrin and C-reactive protein levels correlate well with disease severity (8). Okocha *et al* also identified C-reactive protein as a surrogate marker of disease severity (9). However, despite proven clinical utility of these markers in grading disease severity in patients with SCA, they are not readily available in most laboratories in developing countries, and where they are found, they are expensive, and require expertise and expensive equipment to run. Similarly, some of the clinical parameters used in clinical severity scoring systems require radiological investigations e.g. X-rays for Avascular Necrosis (AVN)/Osteonecrosis, and Ultrasound Scan for Cholelithiasis (8,9,10).

These investigations are also expensive and may not be readily available in primary and secondary healthcare facilities in most developing countries including Nigeria. In addition, there is an over reliance on patient or caregiver recall of clinical events such as frequency of hospitalization and acute crisis due to lack of electronic medical records that could easily allow for recall of previous signs, symptoms, complications and laboratory investigation results.

This study therefore compared the performance of simple and readily available laboratory parameters for a proposed severity scoring system (PropScore) to a pre-existing scoring system.

Materials and methods

Following the acquisition of institutional ethical approval (ABUTH/HREC/K70/2014), a derivation group of 45 SCA patients and a validation group of 300 SCA patients were enrolled into the study. For each phase, participants were consecutively enrolled during steady state (10) while attending sickle cell clinic at Ahmadu Bello University Teaching Hospital, Zaria. This is a premier tertiary health facility in northern Nigeria which provides health services with various specialist care. Haematology department sees a weekly average of 40-50 sickle patients as out patients while an average of 10 patients are admitted either in the Haematology Day Care unit or the Wards. Consenting patients aged ≥ 18 years were enrolled into the study after obtaining informed consent.

History of complications such as acute chest syndrome, chronic leg ulcers, priapism, avascular necrosis, pregnancy losses and socioeconomic status (11) were documented following administration of semi-structured questionnaires. Haemoglobin (Hb) concentration and WBC counts were assessed using automated Haematology analyzer (Sysmex XT 2000i, IL60060, U.S.A). Severity scores were computed for each participant based on the number of complications, haemoglobin levels and white blood cell counts according to the pre-existing scoring system (9) as found in Table 1. A proposed scoring system PropScore was also computed based on Hb level and WBC counts only (Table 2).

Table 1: Pre-existing scoring system proposed by Okocha and colleagues (9)

PARAMETERS	RANGE	SCORE
Hb concentration (g/dL)	≥ 10	0
	≥ 8 to < 10	1
	≥ 6 to < 8	2
	≥ 4 to < 6	3
	< 4	4
WBC count ($\times 10^9/L$)	< 11	0
	≥ 11 to < 15	1
	≥ 15 to < 20	2
	≥ 20	3
Complications		Score of 1 for each complication
Aggregate score	≤ 3	Mild
	4-5	Moderate
	> 5	Severe

Data Analysis

Data were analysed using SPSS version 20. Severity scores were treated as ordinal variables. Spearman rank correlation was conducted to determine any correlations between severity scores and Kappa analyses

Table 2: Proposed scoring system (PropScore)

PARAMETERS	RANGE	SCORE
Haemoglobin (g/dl)	> 10	0
	> 6 to ≤ 10	1
	≤ 6	2
WBC count ($\times 10^9/L$)	≤ 10	0
	> 10 to ≤ 20	1
	> 20	2
Aggregate Score	≤ 1	Mild
	2 - 3	Moderate
	4	Severe

conducted to determine the measurement of agreement between the final gradings of each scoring system. Further analyses using Mann Whitney U, Spearman correlation and Kruskal Wallis were conducted to describe the distribution of the proposed score across categories of gender, age and socioeconomic status respectively. Kappa coefficients of 0.00-0.20, 0.21-0.40, 0.41-0.60, 0.61-0.80, 0.81-1.00 were interpreted to indicate poor, fair, moderate, good and excellent levels of agreement respectively (12). Level of statistical significance was set at ≤ 0.05 .

Results

Derivation Group (n = 45)

The median (IQR) age of the participants was 22 (7) years with females being 33 (73.3%) of the participants. Most of the participants, 39 (86.7%) were diagnosed with SCA between 0-5 years while the remaining were diagnosed at 6-17 years of age. Twenty-two participants (48.9%) were from the medium socio-economic class (Figure 1). The Hb and WBC counts of the participants in this group were 7.3 ± 1.4 g/dl and 11.3 ± 3.0 ($\times 10^9/L$) respectively.

Figure 1: Boxplots showing the relationship between sex and PropScore in derivation

There was a positive, strong and statistically significant correlation between the pre-existing score of Okocha and Colleagues and the PropScore ($p = 0.844$, $p = < 0.001$). There was a strong agreement between the grading by both scoring systems (K value = 0.745, 95% CI 0.564, 0.910, $p = < 0.001$). There was no statistically significant correlation between the PropScore and age ($p = 0.055$,

95% CI -0.243, 0.343, $p = 0.721$. Male participants had higher ProScores compared to females. Also, participants in the medium socio-economic class had relatively higher PropScores compared to those in the high and low classes (**Figure 1 and 2**).

Figure 2: Boxplots showing relationship between socioeconomic status and PropScore

Validation Group (n = 300)

The mean age of the participants was 24.6 ± 7.1 years with females being 188 (62.7%) of the participants. Most of the participants 197 (65.7%) were from the medium socio-economic class with 66 (22.0%) and 37 (12.3%) belonging to low and high socio-economic classes respectively. The mean Hb and WBC counts were 8.1 ± 1.7 g/dL and 11.8 ± 4.2 ($\times 10^9$ /L) respectively.

There was a positive, moderate and statistically significant correlation between the Pre-existing Score and the PropScore ($p = 0.601$, $p = <0.001$). However, there was a weak agreement between the grading by both scoring systems (K value = 0.184, 95% CI 0.115, 0.250, $p = <0.001$). There was no statistically significant correlation between the PropScore and age ($p = -0.031$, 95% CI -0.119, 0.077, $p = 0.599$). Both genders had similar median (IQR) PropScore [2(1) vs 2(1), MWU=10467.000, $p = 0.930$]. There was a statistically significant difference in the distribution of PropScore across socioeconomic groups ($\chi^2 = 7.616$, $df = 2$, $p = 0.022$). *Post hoc* pairwise comparisons are summarized in **Table 3**.

Table 3: *Post hoc* analyses for socioeconomic status and ProScore for validation group

Socio-economic Status	Median (IQR)	MWU Statistic	p-value
Low vs Medium	2(2) vs 2(1)	5334.500	0.022
Low vs High	2(2) vs 1(1)	867.000	0.011
Medium vs High	2(1) vs 1(1)	3287.000	0.318

Discussion:

The PropScore proposes the use of only two parameters; haemoglobin and white cell counts which can be readily determined even in healthcare settings with basic facilities. Haemoglobin and white cell count play major roles in the patho-mechanism of SCA and also serve as markers of disease severity. Low haemoglobin levels and high WBC have been implicated in adult and

and paediatric morbidities such as stroke (infarction), acute chest syndrome and leg ulcers and mortalities (13,14). Conversely, high Hb has been associated with increased acute pain rate and avascular necrosis (15).

In the derivation group, it was found that as the total aggregate score using the pre-existing (Okocha and colleagues) scoring system increases, the PropScore also increased exhibiting a strong positive linear relationship between the 2 scoring systems. Interestingly because correlation does not give adequate information about agreement on individual patients, we further assessed the degree of agreement using Kappa statistics. This demonstrated a strong agreement between the grading systems. Although, our results indicate that there is high agreement between the two scoring systems among the derivation group, there is need to validate such findings. Thus, the reduction in the strength of agreement between the scoring systems when utilized in the validation group suggest that the finding in the derivation should be interpreted cautiously. This does not imply an absence of utility for the PropScore score as the separate scores may have varying scopes of application. Okocha *et al* score has not been validated or assessed to find its effect on quality of life and the likely impact on morbidity and mortality over time. Similarly, we do not know the impact of the proposed score to the earlier mentioned indices.

It is noteworthy that upon validation, the PropScore score did not exhibit any age or gender differences. This suggests that, it may apply equally across the category. However, a prospective study design will need to be conducted to assess any differences in age as well as the evolution of complications.

This study also indicates that patients who belong to the medium and high socioeconomic classes have less severe disease. This may be due to easy access and ability to afford healthcare and possibly, they are less prone to some environmental stressors and have good nutrition that may build up their Hb level.

Although this study is the first of its kind in our setting and it proposes the cheapest scoring system to our knowledge, it is important to note that for now, definitive inferences cannot be made as there is still need to assess the ability of the proposed score to predict quality of life and long-term outcomes. Similarly, indices such as sensitivity, specificity and predictive values of this proposed score will need to be determined using a prospective cohort design.

Conclusion:

There is a poor agreement between the proposed scoring system and the pre-existing scoring system. However, we recommend that the impact of the proposed scoring system on quality of life and long-term morbidity be assessed.

Acknowledgment:

This is to acknowledge the support of Tertiary Education Trust Fund (TETFUND) for providing financial support for these findings to be presented during the 2019 Conference of International Society for Haematology at Vancouver, Canada.

References

1. Pleasants S. Epidemiology: a moving target. *Nature*. 2014;515:S2–3
2. World Health Organization, 63rd World Health General Assembly, Geneva, 17 March 2009 adopted resolution on Recognition of Sick Cell Anaemia as a Public Health problem
3. Ohaeri JU, Shokunbi WA: Psychosocial burden of sickle cell disease on caregivers in a Nigerian setting. *J Natl Med Assoc*. 2002 Dec; 94(12):1058-70.
4. Lal A, Vichinsky PE. Sickle Cell Disease. In: Postgraduate Haematology. Hoffbrand AV, Catovsky D, Tuddenham DGE. eds, 5th edn Blackwell Publishing USA 2005:104-118.
5. McGann PT, Alecia C. N, and Russell E. We: Current Management of Sickle Cell Anemia. *Cold Spring Harb Perspect Med* 2013;3: a011817
6. Bruce F. C, Christian E, Jeffrey S. L, Marilyn H. G, Evaluation Of Clinical Severity In Sickle Cell Disease
7. Tyseer A, Anwaar A.Y.K, Bakhiet A, Azza B, Bahaeldin K. E: Evaluation of Clinical Severity of Sickle Cell Anemia in Sudanese Patients. *American Journal of Research Communication* 2016: Vol. 4(6)
8. Hedo CC¹, Aken'ova YA, Okpala IE, Durojaiye AO, Salimonu LS. Acute phase reactants and severity of homozygous sickle cell disease. *J Intern Med*. 1993 Jun;23 3(6):467-70
9. Okocha E, Onwubuya E, Osuji C, Ahaneku G, Okonkwo U, et al. (2015) Disease Severity Scores and Haemogram Parameters in Nigerian Sickle Cell Disease Patients. *J Blood Disord Transfus* 6: 324.
10. Ballas SK, Lief S, Benjamin LJ, et al. Definitions of the phenotypic manifestations of sickle cell disease. *Am J Hematol* 2010; 85:6–13.
11. Temitope A E, Adeyemi O O, Patricia A A and Ayodeji O E; Socio demographic factors and edentulism: the Nigerian experience. *BMC Oral Health* 2004, 4:3 doi:10.1186/1472-6831-4-3
12. Momeni A, Pincus M, Libien J. Measures of agreement. In; *Introduction to Statistical Method in Pathology*. First edn. Springer International Publishing AG Cham Switzerland 2018; 93-120.
13. W. F. Rosse, M. Narla, L. D. Petz, and M. H. Steinberg, New views of sickle cell disease pathophysiology and treatment, *Haematology*, vol. 2000, no. 1, pp. 2–17, 2000.
14. Buchanan ID, Woodward M, Reed GW. Opioid selection during sickle cell pain crisis and its impact on the development of acute chest syndrome. *Pediatr Blood Cancer* 2005; 45:716–724
15. Adams RJ. Stroke prevention and treatment in sickle cell disease. *Arch Neurol*. 2001;58(4):565-568. doi:10.1001/archneur.58.4.565