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Bone Marrow Morphology: A Key Diagnostic Tool in Various Hematological and Non Hematological Disorders

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ABSTRACT

Bone marrow morphology means microscopic examination of bone marrow cells and tissue samples obtained by aspirate and trephine biopsy. An invaluable tool for diagnosis of many hematological and non-hematological disorders, various types of cancer staging and metastases detection. Different kinds of anemia and leukemia can be accurately diagnosed and monitored. **Objective:** To check the spectrum of diseases which could be identified and diagnosed with the help of bone marrow morphology examination thus demonstrating its diagnostic utility and to check diagnostic concordance between aspirate and core biopsy. **Methods:** Cross sectional study with consecutive sampling technique conducted over period of one year. Samples of both Bone Marrow Aspiration (BMA) and trephine biopsy (BMB) were collected from all patients included in study after consent using standard protocols. Air dried smears were prepared from bone marrow aspiration samples while trephine biopsy tissues were processed by histopathological techniques. Routine staining such as Wright Giemsa stain, H and E stain and special cytochemistry were used to visualize the cellular architecture of bone marrow. **Results:** Out of 471 samples, males were predominant with the frequency of 63.9% and maximum patients (31.8%) were from the age group of 35-40 years. Most common clinical indication to conduct bone marrow examination was unexplained Cytopenia which accounted for 35.2% cases, followed by suspicion of Leukemia (28.5%). Malignant hematological disorders were more common as compared to benign disorders (64% vs 17.5%). Acute leukemia was the most commonly identified cancer with frequency of 27.6%. **Conclusions:** Bone marrow morphology till date remains low risk, economical, crucial diagnostic tool in especially in under resource country like Pakistan. It can guide physicians to plan proper and timely management of patients.

INTRODUCTION

Bone marrow morphology examination, including aspiration and trephine biopsy, remains a cornerstone of Hematopathology being a key tool in diagnosis of various hematological and non-hematological disorders despite the advancements in molecular and genetic diagnostics. Composition of the bone marrow depicts the presence of Hemopoietic stem cells with Erythroid, Myeloid, Megakaryocytic lineage cells, adipose cells and stromal cells which are supportive microenvironment in nature [1]. Bone marrow aspirate shows complete cytological details whereas trephine biopsy gives panoramic view of bone marrow architecture. Different sites are used for the sampling of bone marrow among which the most preferred site is posterior superior iliac spine. However, in infants, ideal site of bone marrow sampling is medial side of upper end of the tibia, slightly below the level of tubercle of tibia [2]. The standard approach to diagnosis of many different hematological and non-hematological disorders, is still based on bone marrow morphology assessment under light microscopy especially various malignant disorders like Acute and Chronic Leukemia, Lymphoma, bone marrow metastatic disease showing particular percentage of malignant hematopoietic cells or malignant secondaries of primary neoplasm arising from any other organ in body apart from bone marrow [3]. Though, the examination of bone marrow is a common procedure in the west and has been the primary diagnostic tool for hematological malignancies and other blood disorders. However, in

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Pakistan only major medical institutions such as those in Karachi, Lahore, and Rawalpindi, likely have been among the early adopters of this procedure. Bone marrow examination must be preceded by complete clinical assessment of the patient including clinical history, baseline hematological examination including complete blood count and peripheral smear examination followed by targeted radiological, microbiological and biochemical investigations if required [4]. Bone Marrow Aspirate (BMA) is a diagnostic procedure that involves extracting a small amount of liquid bone marrow for examination under light microscope after air dried smears are stained with routine Wright Giemsa stain. Information obtained from Bone Marrow Aspiration includes overall bone marrow cellularity including exact percentage of hematopoietic / abnormal cell counts, which can help in differentiating between proliferative and hypoplastic bone marrow disorders like Myelodyplasia and Aplastic anemia respectively [5]. It can also give significant information about morphological/ cytological detail about size, shape, cellular outline, cytoplasm and nuclei of different cells under investigation such as characteristic appearance of Lymphoblast, Myeloblast and other malignant Plasma cells, thus enabling Pathologists (Hematologists) to correctly diagnose different types of acute lymphoid leukemia, acute myeloid leukemia and plasma cell myeloma respectively [6]. Bone marrow aspirate smears can also be used for cytochemical staining such as Sudan Black B (SBB), Myeloperoxidase (MPO), Periodic Acid Schiff (PAS), Specific and Nonspecific Estrases (NSE) etc., which can help in classifying different types of Leukemia. Bone marrow aspirate can also be used for diagnosis of different infectious diseases by doing bone marrow aspirate cultures and sensitivity. Bone marrow morphology examination after staining aspirate smears with another special stain i.e., Perl's stain is still gold standard for diagnosis of Iron Deficiency anemia [7]. Bone Marrow Trephine Biopsy (BMB) is a diagnostic test where a small core tissue of bone marrow is removed for examination under microscope. It complements the information obtained from a bone marrow aspiration. Its examination under light microscopy gives detailed panoramic view of bone marrow cellularity and provides comprehensive overview of inflammatory cells percentage, presence of any extra medullary cells, dysplasia, and cellular atypia, patterns of infiltration by malignant lymphoma, metastatic disease, marrow packing with blasts and any degree of fibrosis. Presence of Histiocytosis, and Storage disorders are clearly diagnosed on trephine biopsy [8]. Granulomatous disease is another difficult diagnosis detected by trephine biopsy. Bone marrow trephine biopsy has another advantage that its can be used for another important diagnostic modality that is immunohistochemistry to study confirmation of diagnosis, extent of bone marrow infiltration and prognosis of many malignant neoplasms. Two pillars of bone marrow morphology exam such as Bone marrow aspirate and trephine biopsy are both complementary to each other however sometimes aspirated specimen is of very low volume and sometimes it is diluted with sinusoidal blood, in both these conditions bone marrow aspirate is devoid of cellular components and suboptimal for reporting [9]. Adequate core length trephine biopsy makes it ideal technique for providing information regarding marrow cellular and architectural changes occurring in marrow cavity due to various underlying malignant and nonmalignant processes.

Therefore, aim of present study was to check the spectrum of diseases which could be identified with the bone marrow examination at initial stages. Frequency and categorization of benign and neoplastic lesions were also checked to compare diagnostic concordance between BMA and BMB.

METHODS

The present study was conducted at the Pathology department (Hematology section) of King Edward Medical University/Mayo Hospital Lahore over the study period of one year from March 2023 to March 2024. Ethical approval was taken from the institute Ethical Review Board (Reference Number: 329/RC/KEMU). It was cross sectional study and samples were collected through consecutive sampling technique. Sample size was calculated by using win-pepi ver: 11.15 software with confidence level of 95%, acceptable difference = 0.05 [2]. A Total of 471 cases which fulfilled the inclusion criteria were selected in the study period. Inclusion criteria included cases from the both gender of age groups (1-60 years) in the study. All the patients that were referred for examination of bone marrow and also for staging of hematological malignancies were included in the current study. Exclusion criteria defined as diluted bone marrow aspirate and samples from the patients less than 1 year of age were excluded from the study. Demographic data like age and gender were recorded from all the included cases. Clinical indications were determined by taking into account, patients thorough clinical history and on the basis of complete blood count CBC and peripheral smear results. Both BMA and BMB were taken from each patient according to standard ICSH (International council for standardization in Hematology) protocol of bone marrow sample collection [5]. Written informed consent was taken from each patient before the procedure. Bone marrow aspirate was done from posterior iliac crest using aseptic techniques. Anterior superior iliac spine was used for the bone marrow sample collection from obese patients. Selected area from where the sample was taken was locally anesthetized first and then commercial

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bone marrow needle (with removable stylet) of appropriate size was used to take small amount (0.5ml) of bone marrow aspiration followed by collection of bone marrow trephine biopsy sample placed in Bouin's solution. Air dried smears were made from the bone marrow aspirate while for trephine biopsy, (>1cm) biopsy on gross examination was considered adequate. For the processing of bone marrow aspirate, a mono-layered smear was made from the concentrated marrow cells on the slide. After air drying, methanol was used to fix the smears. Slides were stained with Wright-Giemsa stain which contain methylene blue and eosin dissolved in methanol. After staining, slides were air dried and were observed under light microscope Olympus CX43 five head Microscope using 10x, 20x, 40x and 100x magnification by counting 400 cells to visualize the cytological detail and infiltration pattern of the bone marrow. For processing of bone marrow trephine biopsy, samples were initially decalcified. After this, samples were processed according to standard histopathological techniques including tissue processing and embedding in paraffin wax. Special stains such as Sudan Black B, Non-Specific Esterase (NSE), Acid Phosphatase, Periodic Acid Schiff (PAS), Reticulin stain was used according to the patient's clinical symptoms and probable disease identification. Photomicrographs were taken by digital camera attached to Olympus CX43 five head light microscope EP50 with 2592x1944 pixel resolution. Normal morphology of bone marrow was distinguished from pathological bone marrow by the presence of abnormal cells infiltrate in latter. Acute Leukemia was diagnosed and differentiated into Acute Lymphoblastic (ALL)and Acute Myeloblastic Leukemia (AML) according to WHO 2016 diagnostic criteria stating presence of 20% Bone marrow aspirate Blasts and classified according to FAB morphological classification by using special staining methods (SBB, MPO, PAS, AP, NSE) and subtyped by using immunohistochemistry on trephine biopsy. Similarly, remission assessment was done morphologically according to percentage of bone marrow blast (<5%). Chronic leukemia such as Chronic Myeloid Leukemia (CML) was diagnosed morphologically according to WHO 2022 criteria defined by Granulocytic Hyperplasia with variable number of blasts according to different stages of disease. Lymphomas were differentiated on the basis of morphologically different atypical lymphoid population and subtyped by immunohistochemistry. Multiple Myeloma was differentiated due to presence of >10% abnormal plasma cells in bone marrow morphology as part of WHO 2016 diagnostic criteria. MPN especially Myelofibrosis was one of the disorders that can only be diagnosed on bone marrow examination with Reticulin special stain. Non hematological metastatic disease was differentiated from hematological malignancies using specific morphology of malignant cells and use of immunohistochemistry [9]. Amongst Benign Hematological disorders, Dimorphic anemia was differentiated from Megaloblastic anemia by presence of two different erythroid maturation pattern with special stain (Perl's stain) used to diagnose iron deficiency anemia. Hypoplastic bone marrow disorders showed less than 20% cellularity in BMB exam. Malaria infection showed ring forms and gametocytes in bone marrow, Leishmania infection exhibited LD bodies in bone marrow while tuberculous granulomatous disease was differentiated on marrow morphology showing giant epitheloid cells and inflammatory cell infiltrate. While bone marrow aspirate culture isolated salmonella typhi. Storage disorders showed bone marrow infiltration by large histiocytic gaucher cells and foam cells. Data were collected and statistically analyzed by using SPSS software 27.0. Numerical data were expressed as mean. Frequencies and percentages were calculated for the univariate variables. Diagnostic concordance was the rate of agreement between BMA and BMB was expressed as percentage. Chi square test was used to evaluate any statistically significant difference between BMA and BMB.

RESULTS

A total of 471 samples of bone marrow aspiration and trephine biopsy for bone marrow morphology examination was processed during the study period. Out of which 63.9% (n=301) samples were collected from the male patients while 36.1% (n=170) samples were collected from the female patients. Age distribution showed that maximum samples were collected from the age group of 30-45years n=150, followed by age group of 45-60yrs and 15-30yrs (n=100) each table 1.

Table 1: Age Distribution of Patients

Age Group	Frequency (%)
Less than 15 Years	50 (10.6%)
15-30 Years	100 (21.2%)
30-45 Years	150 (31.8%)
45-60 Years	100 (21.2%)
More than 60 Years	71 (15.2%)
Total	471 (100%)

Most common clinical indication identified for which bone marrow examination was done, found to be Bi-Pancytopenia (35.2%, n=166) followed by suspected diagnosis and remission assessment of Leukemia including acute and chronic leukemia's (28.5%, n=134). Other common indications were summarized in table 2.

Table 2: Clinical Indications for which Bone Marrow Examination was done

Clinical Indications to Perform Bone Marrow	Frequency (%)
Evaluation of Cytopenias (Bi and Pancytopenia)	166 (35.2%)
Assessment of Anemia	53 (11.3%)
Diagnosis and Remission Assessment of Leukemia's	134 (28.5%)
Leucoerythroblastic Blood Picture	20 (4.2%)
Fever of Unknown Cause	64 (13.6%)
Thrombocytopenia	34 (7.2%)

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Most frequent complications associated with the sampling of bone marrow aspirate and bone marrow trephine biopsy were pain, anxiety, bleeding and dizziness. About 90% in individuals feel pain during the procedure in spite of the local anesthesia. While ratio of dizziness and bleeding was too low as compared to pain which was 1.09% and 1.82% respectively. Total 471 samples of bone marrow examination were processed for the identification of hematological and non-hematological diseases by using Giemsa and special stains. 72 samples showed normal bone marrow cellular architecture. Most common clinical condition observed was Leukemia (both acute and chronic leukemia/Lymphomas) which was 48.8% (n=130), followed by Remission of malignant tumors 11.8% (n=56). Detailed disease pattern observed in bone marrow examination was summarized in table 3.

Table 3: Disease Spectrum Observed in Bone Marrow Morphology Examination

Disease Pattern (Clinical Diagnosis)	Frequency (%)
Malignant Hematological Disorders	
Acute Leukemia	130 (27.6%)
Chronic Leukemia/Lymphoma	100 (21.2%)
Multiple Myeloma	11 (2.3%)
Myelofibrosis	5 (1.1%)
Remission of Malignant Tumors	56 (11.8%)
Non-Malignant Hematological Disorders	
Erythroid Hyperplasia	6 (1.3%)
Megaloblastic Anemia	21 (4.5%)
Dimorphic Anemia	6 (1.3%)
Hypoplastic Marrow	33 (7%)
ITP*	10 (2.1%)
Infective Pathology	6 (1.3%)
Non-Hematological Malignant Disorders	
Metastasis Staging	9 (1.9%)
Distribution of other Conditions	
Normal Study	72 (15.3%)
Storage Disorders	6 (1.3%)
Total	471 (100%)

*Idiopathic Thrombocytopenic Purpura

In this study, bone marrow morphology showed four peculiar fatal disease patterns requiring urgent diagnosis and adoption of early treatment plan. These four particular disorders can only be diagnosed and visualized through bone marrow exam. Photomicrograph A shows BMA stained with SBB special stain showing Acute leukemia classified as AML with maturation according to FAB classification. Rapid diagnosis with minimum cost was essential for patient as it was deadly disease and early management plan was extremely important especially in under resource country like Pakistan. Photomicrograph B shows a rare finding of presence of bone marrow Calcium Oxalate crystals in a patient who presented with cytopenias (anemia, platelet dysfunction) and bone pains. It's crucial to start early and individualized treatment. Photomicrograph C shows Myeloproliferative disorder (MPN-ET). This patient presented with portal vein thrombosis and thrombocytosis. Without bone marrow morphology, diagnosis of this disease was not possible without timely bone marrow exam showing characteristic large megakaryocytes with abundant cytoplasm and lobulated, stag horn nuclei. Photomicrograph D shows Bone marrow metastatic disease. In this disorder bone marrow trephine morphology was mandatory for staging of disease, without which treatment can't be started (Figure 1).

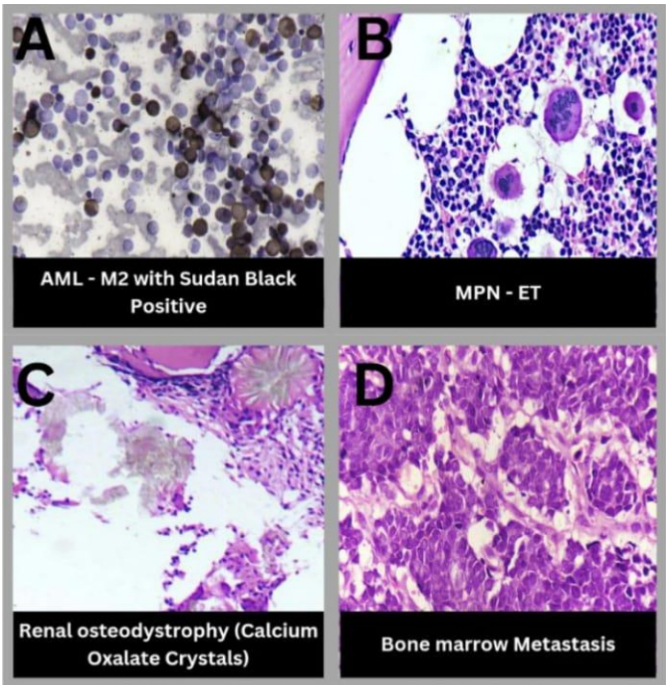

Figure 1: A: AMLM2 with SBB Positive B: MPN-ET (Essential Thrombocythemia) C: Calcium Oxalate Crystal (Renal Osteodystrophy) D: Bone Marrow Metastasis

Photomicrographs were taken by digital camera attached to Olympus CX43 five head light microscope EP50 with 2592x1944 pixel resolution. In present study, diagnostic concordance rate between BMA and BMB for diagnosis of various disorders was 88% while only 27 cases were missed on BMA alone and was diagnosed on BMB making diagnostic disagreement between both tools of bone marrow morphology almost negligible as depicted in table 4.

Table 4: Diagnostic Concordance between BMA and BMB

Disease Pattern (Clinical Diagnosis)	Frequency (%)
Malignant Hematological Disorders	
Acute Leukemia	130/130 (100%)
Chronic Leukemia/Lymphoma	93/100 (93%)
Multiple Myeloma	11/11 (100%)
Myelofibrosis	3/5 (60%)
Remission of Malignant Tumors	51/56 (91%)
Non-Malignant Hematological Disorders	
Erythroid Hyperplasia	6/6 (100%)
Megaloblastic Anemia	21/21 (100%)

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Dimorphic Anemia	6/6 (100%)
Hypoplastic Marrow	4/33 (%)
ITP*	10/10 (100%)
Infective Pathology	5/6 (83%)
Non-Hematological Malignant Disorders	
Metastasis Staging	5/9 (55%)
Distribution of other Conditions	
Normal Study	71/72 (98%)
Storage Disorders	2/6 (33%)
Total	418/471 (88%)

Comparison of the cases diagnosed by bone marrow aspirate and bone marrow trephine biopsy was statistically done by using Chi-square test. Diagnosed cases and missed diagnosis in both modalities were compared which showed statistically significant value of 0.012. This table showed there was a statistically significant difference between BMA and BMB diagnosis ($p < 0.05$). This means that the proportion of diagnoses being done or missed were statistically different between BMA and BMB, which shows the complementary nature of both modalities in bone marrow morphology interpretation (Table 5).

Table 5: Comparison of Cases Diagnosed in BMA and BMB

Cases	Diagnosis Done (Positive)	Diagnosis Missed (Negative)	Total	p-Value (Chi Square Test)
BMA	444	27	471	0.013
BMB	460	11	471	

Chi-Square Statistics: 6.1699, p-value: 0.0130

DISCUSSION

Bone marrow examination including both aspiration and trephine biopsy were considered complementary to each other and were very important and valuable tools for the identification of malignant as well as non-malignant hematological conditions [9]. Certain non-hematological conditions such as renal osteodystrophy - Calcium Oxalate crystals, Bone Marrow Metastasis can only be identified by bone marrow examination when performed after comprehensive morphological assessment of the selected patients [8]. Generally, it was amalgamation of different hints collected from the observations of different morphological parameters that eventually leads to exact diagnosis [10]. In the present study, total 471 bone marrow samples were examined from the patients of both genders and different age groups. Out of total samples, male gender outnumbered the female gender with the frequency of 63.9% and 36.1% respectively. Similar results were reported by Kumar V *et al.*, in which majority of the patients were males [11]. Another study also reported the predominance of males suffering from different hematological disorders as compared to females [12]. In this study, the age range of this study participants were from 1 years to more than 60 years. Similar to these results were reported by Pudasaini S *et al.*, Kibria SG *et al.*, and Mahfuz H *et al.*, which showed that maximum patients were from age group of 31-45 years [13-15]. Comparable to this results, two other studies also reported the similar findings [16, 17]. Various indications were observed in the current study for bone marrow examination, among which work up for the cytopenia and probability of different hematological malignancies were found to be the most common diagnosis from bone marrow morphology examination. In the present study, most common indication was cytopenia (35.2%, n=166), followed by identification of leukemia both acute and chronic leukemia (28.5%, n=134). In accordance to this results, Ahmed SQ *et al.*, also reported cytopenia as a common indication which was 38.3% [18]. Similar results were also reported by Pudasaini S *et al.*, in which cytopenia accounted for 22.8% of the total cases [13]. However, Gandapur AS *et al.*, (22.8) and Bashawri LA (11.9%) reported Cytopenia as the 3rd common indication for bone marrow examination in their studies [16, 19]. Major disease burden in this study comprise of malignant hematological and non-hematological disorders, for which bone marrow morphology examination was first and foremost requirement. In this study, out of 471 samples, only 15.3% (n=72) showed normal cellular architecture while 1.0% (n=6) were storage disorders including Gaucher disease and Nieman Pick disease. Bone marrow was infiltrated by characteristic abnormal histiocytic cells in storage disorders [20-22]. Paediatric patients included in this study constitue around 10%, mainly showed bone marrow infiltration by Acute Leukemia and storage disorders. These clinical conditions were debilitating and require early detection made possible by bone marrow Morphological exam. Moreover, bone marrow infiltration was part of diagnostic criteria in these disorders [23]. So here diagnostic usefulness of bone marrow morphology was clearly visible. Malignant hematological conditions accounted 64% (n=302) which were more predominant than non-malignant hematological conditions (17.5%, n=82). Comparable to this results, Mahfuz H *et al.*, from Bangladesh reported the predominance of hematological malignancies in his study (64.2%) than non-malignant conditions which were 22.4% [15]. In accordance to this results Chowdhury MRK also reported the high prevalence of malignant hematological diseases than non-malignant hematological conditions [1]. Majority of malignant cases were identified as acute leukemia (27.6%, n=130) in this study. Various other studies also reported the similar results [12, 20]. Multiple myeloma was identified in 2.3% (n=11) of cases of bone marrow examination. Comparable to these results, two different studies also reported 2.5% and 3.5% rate of multiple myeloma diagnosis through bone marrow examination [2, 14]. Among non-malignant hematological conditions, hypocellular marrow was observed in 7% (n=33) of cases. Another study also reported similar results with the percentage of 5.3% [13]. It's important to mention here that aplastic anemia and other hypocellular bone marrow syndromes can only be

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confirmed by bone marrow morphology on BMB [7]. In this study, megaloblastic anemia was identified in 4.5% (n=21) cases of bone marrow examination. Bashir *et al.*, Mahfuz H *et al.*, and Yadav S *et al.*, reported 8%, 2.63% and 6.5% frequency of megaloblastic anemia respectively [2, 15, 21]. Pudasaini S *et al.*, reported 12.3% frequency of megaloblastic anemia which was slightly higher than this study and could be attributed to the nutritional deficiencies of their native population [13]. Swift bone marrow morphological assessment and prompt treatment of megaloblastic anemia is mandatory as failure can lead to irreversible neurological damage in the form of sub-acute combined degeneration of spinal cord [24]. Less than 1.0% samples were found to be inadequate in this study, which were in accordance with the study by Ranabhat S *et al.*, who reported inadequacy of 0.87% samples in his study [9]. In this study, diagnostic agreement between BMA and BMB was around 89%, which was in accordance with Meenu Gilotra M *et al.*, who reported concordance rate as 87% [22].

CONCLUSIONS

Bone marrow morphology examination was a time-tested and valuable diagnostic tool in clinical practice, especially in resource-limited settings. It was relatively simple, cost-effective and has ability to provide a wealth of information regarding blood cells pathology, making it crucial in diagnosing and understanding etiopathogenesis of broad spectrum of blood disorders. In developing countries like Pakistan where access to advanced medical technologies such as flow cytometry, cytogenetic and molecular genetics were limited due to cost and lack of infrastructure, and not in reach of majority of population, bone marrow morphology serves as a reliable and accessible diagnostic as well as prognostic tool, aiding in prompt and accurate treatment for improved patient outcomes.

Authors Contribution

Conceptualization: MA
Methodology: RM, MA
Formal analysis: HS, SA
Writing, review and editing: MA, SA, RM, HS

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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