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Adult type CML in paediatric age group – a case series from tertiary care hospital

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ABSTRACT

Chronic myeloid leukaemia is a clonal disorder arising from hematopoietic stem cell, affecting all the lineage of haematopoietic stem cells. The average age of affection in chronic myeloid leukemia is 60 to 65 years and is extremely rare in childhood comprising 3% of paediatric leukaemia. An institution-based study was carried out to reveal the statistics of pediatric chronic myeloid leukaemia patients in a tertiary health care centre of North India serving mainly the economically under privileged population belonging to minority groups.

Key words: Chronic myeloid leukaemia; Clonal, Hematopoietic; North Indian population; Paediatric

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INTRODUCTION

Chronic myeloid leukaemia is a clonal disorder arising from hematopoietic stem cell, affecting all the lineage of the same. Haematological findings characteristic of CML are leucocytosis predominantly constituted by middle order cells of granulocytic lineage, hyperplasia of myeloid lineage in bone marrow and extramedullary haematopoiesis,[1] along with infiltration of the red pulp cords by mature and immature granulocytes[2] leading to splenomegaly. The average age of affection in chronic myeloid leukaemia is 60 to 65 years in Western registries,[3] whereas in Indian scenario it typically affects 40 to 60 years age group individuals,[4] through 20 decades earlier than western registries yet it is extremely rare in paediatric age group even in India. The disease accounts to an annual incidence of 1 per million constituting 2% of all leukaemias in children younger than 15 years and 9% of all leukaemia in adolescents between 15 and 19 years, with an annual incidence of 2.2 cases per million in this age group.[5]

Aims and Objectives

An institution-based study to reveal the statistics of paediatric chronic myeloid leukaemia patients in a tertiary health care centre of North India serving mainly the economically under privileged population belonging to minority groups.

Settings and design

It is a retrospective analysis conducted to assess paediatric CML in a tertiary health care centre serving mainly the economically under privileged population belonging to minority groups. Data was collected and analysed from the haematology section of the department of pathology in Era's Lucknow Medical College and Hospital between June 2017 to May 2020.

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MATERIALS AND METHODS

Inclusion criteria

Patients who aged 18 years or less and diagnosed as Ph chromosome-positive CML with BCR-ABL1 fusion gene were included in the study.

Exclusion criteria

Patients more than 18 years of age.

INVESTIGATION

At this tertiary care centre, any suspected CML patients underwent complete clinical as well as laboratory investigations including complete hemogram with differential counts, abdominal sonography (to measure spleen size), bone marrow aspiration and conventional cytogenetic analysis along with RT-qPCR was done from peripheral blood (PB). Immunophenotyping was done if blast cells were present.

OBSERVATIONS

Case 1

A 7 years old boy presented to paediatric OPD complaining on and off fever for 4-5 months along with sense of heaviness in the abdomen in the last 1 month. The patient was well immunized as per schedule. On further evaluation, pallor was found with mild hepatomegaly measuring 7 CMS from the lowest coastal margin and huge splenomegaly of 18 CMS was noted. The patient was admitted in paediatric ward with differential diagnosis of hepatosplenomegaly for e.g., malaria, haemolytic anaemia or tropical splenomegaly. Routine hemogram was carried out, which revealed anaemia with haemoglobin of 5.1 gm/dl. On peripheral smear (Figure 1), blood picture showed leukemic leucocytosis with a count of 1,88,000/dl. Middle order cells of myeloid lineage were seen predominantly in differential leucocyte count including myelocytes (11%), metamyelocytes (07%) and band cells (21%). A few myeloblasts (02%) along with promyelocytes (02%) were also seen. Among mature cell population polymorphs (50%), lymphocytes (02%) monocytes (02%) and eosinophils (01%) were seen. Prominent basophilia with an absolute count of 3760/dl (02%) was also observed. Platelet count was 2,80,000/dl. An impression of Chronic Myeloproliferative Disorder (Chronic Myeloid Leukaemia-Chronic Phase) was made and patient had advised for bone marrow and karyotyping.

Aspiration smears from bone marrow (Figure 2) showed hypercellularity. Hypercellularity was due to myeloid hyperplasia showing increase in predominantly middle order cells of the lineage. Myeloblast constitutes less than

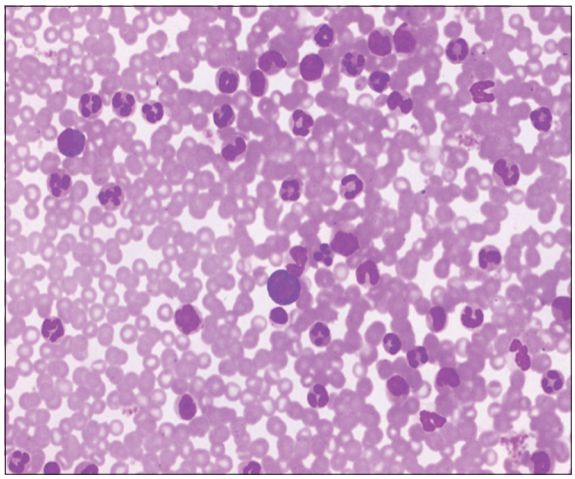

Figure 1: Leishman 40X PBS of CML showing left shift of myeloid series having promyelocyte, metamyelocyte, band form and mature neutrophils

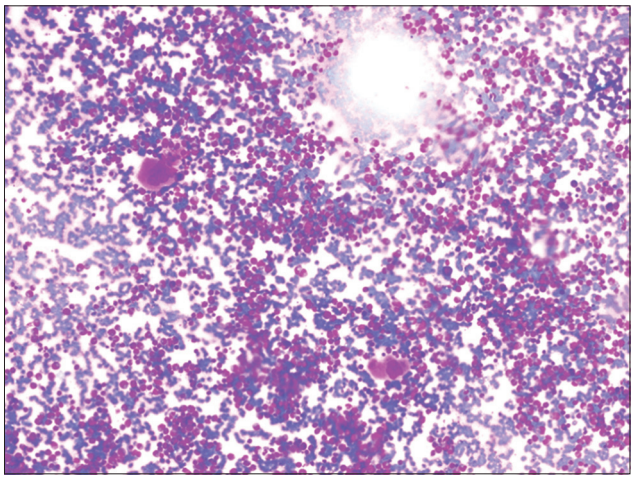

Figure 2: Leishman 10X BM aspiration in CML showing hypercellular marrow with left shift of myeloid series and increased M:E ratio. Fat cells and Megakaryocytes are seen

03% of the entire myeloid precursors excluding the blast phase of the disease. Erythropoiesis was normoblastic with respect to the sequence of maturation but markedly suppressed due to marked increase in myelopoiesis. This led to disproportionately high myeloid erythroid ratio (32:1). Plenty of megakaryocytes with normal morphology were seen showing active platelet formation. Plasma cells along with few lymphocytes were also seen. Thus, the aspiration smear was correlative to the findings of peripheral blood smear picture and were suggestive of Myeloproliferative neoplasm (CML- Chronic phase). Karyotyping for chromosomal analysis was performed for further confirmation, which showed 46, XY, {t(9q;22q)} on a total of 10 metaphases. Philadelphia chromosome positivity (100%) were found in all metaphases, thus translocation 9q; 22q was confirmed in all the metaphases. Real Time RT-PCR assay was done for quantification which

showed that specimen had 67.45% (high) Major BCR-ABL fusion transcript (210).

Case 2

The second case of ours was an 11 years old boy who presented to paediatric OPD with complain of excessive abdominal fullness and extreme loss of appetite leading to almost an emaciated child who looks like of an age of hardly 6 or 7 years. He was perfectly alright 7 months back when he developed an episode of diarrhoea which was also associated with fever. That ailment got relieved by medications but mother noticed some abdominal fullness which gradually increased and made the abdominal wall very tensed. Though patient never complained of pain and tenderness, yet had some abdominal discomfort and decreased appetite. On clinical examination paediatrician noticed mild pallor and a huge splenomegaly. Other signs of malnourishment like decreased subcutaneous fat, cheilosis, flaky paint dermatosis was also found. Patient was also not fully immunised. In paediatric IPD, boy was admitted with differential diagnosis of protein energy malnutrition, haemolytic anaemia, malaria and kala-azar. Patient blood sample was sent for routine investigations. Routine hemogram revealed Hb-3.4 gm/dl. Peripheral blood smear (Figure 3) examination showed leukemic leucocytosis (2,00,000/dl) with predominantly middle order cells of myeloid lineage including myelocytes (21%), metamyelocytes (13 %) and band cells (12%). Occasional myeloblasts (1%) and promyelocytes (02%) were also seen. Among mature cell population polymorphs were predominantly seen (40%) followed by lymphocytes 03% monocytes 03% and eosinophil (01%). With an absolute basophil count of 8000/dl (04%); basophilia was fairly evident in the case. Platelet count was adequate (3,75,000/dl). A preliminary diagnosis of Myeloproliferative Neoplasm (Chronic Myeloid Leukaemia -Chronic Phase) was made. He was advised for bone marrow examination with cell karyotyping and cytogenetic analysis.

Bone marrow aspiration smears showed hypercellularity with predominantly myeloid hyperplasia. Myeloblasts and promyelocytes constituted almost 03 % of the nucleated cell population, thus excluding blast crisis stage of the disease. Basophilic myelocytes and metamyelocytes were also seen in plentiful amount but were not in the range of accelerated phase. Erythropoiesis was suppressed because of markedly increased myelopoiesis but was normal with respect to sequence of maturation which led to quite high M:E ratio of 22:1. Plenty of megakaryocytes having normal morphology with active platelet formation were seen. Thus, aspiration picture was consistent with that of peripheral blood smear and a diagnosis of Chronic Myeloid Leukaemia in chronic phase was made. Chromosomes were

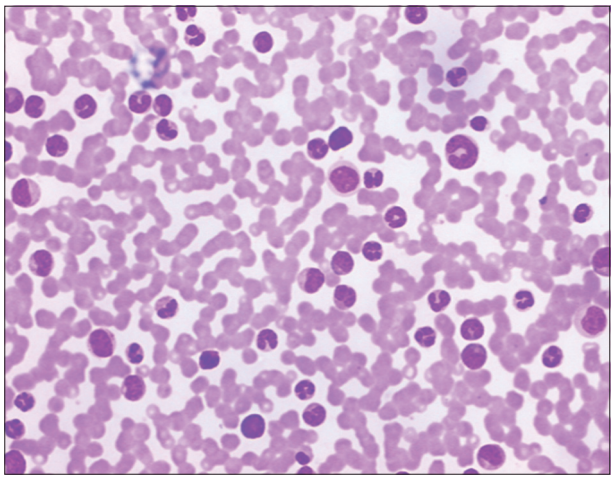

Figure 3: Leishman 40X PBS of CML showing left shift of myeloid series having promyelocyte, metamyelocyte, band form and mature neutrophils

analysed by karyotyping on total of 10 metaphases showing 46, XY, t(9q;22q). All metaphases showed positivity for Philadelphia chromosome (100%).

Minor Groove Binder Real Time RT-PCR assay, done for quantification of hybrid transcript showed that specimen contained 66.25% (high) 210 kDa protein of major BCR-ABL fusion transcript.

Case 3

A ten years old girl presented to paediatric OPD with chief complain of constant dragging sensation on the left side of the abdomen with hard lump felt in the abdomen towards the left side is the third case of the series. She was perfectly alright 5 months back when she started feeling dragging sensation while climbing the stairs followed by an episode of fever. Fever got relieved by medications but dragging sensation persisted. On clinical examination paediatrician noticed mild pallor and a massive splenomegaly. She was admitted in paediatric IPD with a differential diagnosis of haemolytic anaemia, malaria and kalaazar. Patient blood sample was sent for routine investigations. Routine hemogram revealed anaemia (Hb 4.6 gm/dl). Peripheral blood smear examination showed normocytic normochromic anaemia. Total leukocyte count showed leukemic leucocytosis (2,38,000/dl) with predominantly middle order cells of myeloid lineage (Figure 4,5) comprising of myelocytes, metamyelocytes and band cells (49%). Occasional myeloblasts (01%) and promyelocytes (02%) were also seen. Neutrophils (36%) followed by lymphocytes (03%), monocytes (04%) and eosinophils (02%) were seen among mature cell population. Basophilia with an absolute basophil count of 7140/dl (03%) was also predominantly observed. Platelet count was 2,50,000/dl. A preliminary diagnosis of Myeloproliferative Neoplasm (Chronic Myeloid Leukaemia -Chronic Phase) was given

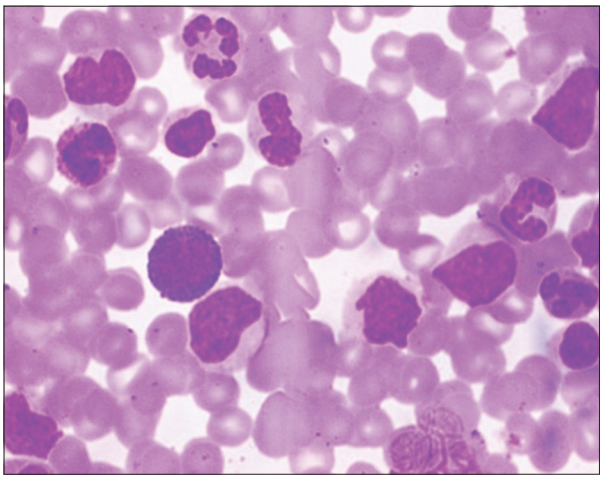

Figure 4: Leishman 100X PBS of CML showing Basophils, promyelocyte, myelocyte, metamyelocyte and segmented neutrophils

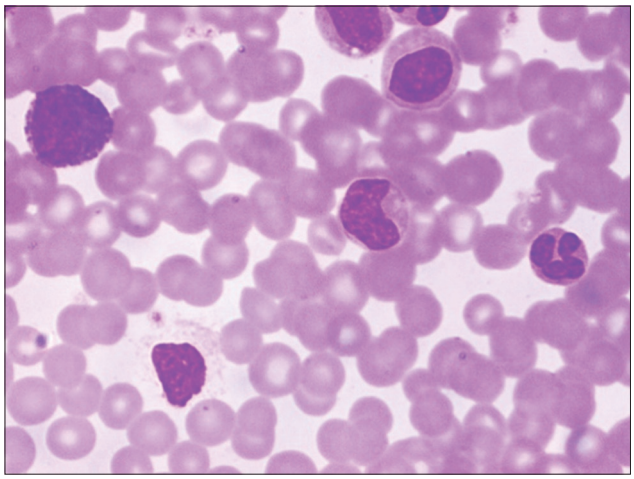

Figure 5: Leishman 100X PBS of CML showing Basophils, promyelocyte, myelocyte, metamyelocyte and segmented neutrophils

with an advice of bone marrow examination with cell karyotyping and cytogenetic analysis.

On bone marrow examination, smears were hypercellular with marked increase in numbers of middle order cells of myeloid lineage. Myeloblasts and promyelocytes constituted almost 03% of the nucleated cell population, thus excluding blast crisis stage. Basophilic as well as eosinophilic myelocytes and metamyelocytes were also seen in plentiful amount but was not in the range of accelerated phase. Erythropoiesis was suppressed because of markedly increased myelopoiesis but was normal with respect to sequence of maturation. Therefore M:E ratio was quite high 12:1. Megakaryocytes were plentiful with normal morphology and showed active platelet formation. Thus, aspiration picture was consistent with that of peripheral blood smear and suggestive of Chronic Myeloid Leukaemia in chronic phase.

Chromosomes were analysed by karyotyping on total of 10 metaphases showing 46, XY, t (9q;22q). All metaphases showed positivity for Philadelphia chromosome (100%).

Minor Groove Binder Real Time RT-PCR assay, done for quantification of hybrid transcript showed that specimen contained 67.25% (high) 210 kDa protein of major BCR-ABL fusion transcript.

Case 4

The fourth case was a six years old boy presented to paediatric OPD for a trauma injury. Paediatrician found a hard lump into the abdomen as an incidental finding, which on further evaluation came out to be a huge spleen in the abdominal cavity. On careful examination it was found that the patient had mild sternal tenderness also since long which the parents were not able to remember. And was also suffering from on and off fever which was so mild that parents were not taking it into account. On clinical examination paediatrician also noticed mild pallor. He was admitted in paediatric IPD with a differential diagnosis of haemolytic anaemia. Patient blood sample was sent for routine investigations. Routine hemogram revealed Hb 6.1 gm/dl. Peripheral blood smear examination showed leukemic leucocytosis (2,50,000/dl) with predominantly middle order cells of myeloid lineage in differential cell count including myelocytes (20%), metamyelocytes (17 %) and band cells (14%). Occasional myeloblasts (02%) and promyelocytes (02%) were also seen. Among mature cell population polymorphs were predominantly seen (33%) followed by lymphocytes (02%), monocytes (04%) and eosinophil (01%). Prominent basophilia with an absolute basophil count of 12500/dl (05%) was also observed. Platelet count was 6,00,000/dl showing thrombocytosis. A preliminary diagnosis of Myeloproliferative Neoplasm (Chronic Myeloid Leukaemia -Chronic Phase) was given with an advice of bone marrow examination with cell karyotyping and cytogenetic analysis.

Bone marrow aspiration (Figure 6) showed hypercellular smears with marked increase in numbers of middle order cells of myeloid lineage. Myeloblasts and promyelocytes constituted almost 03 % of the nucleated cell population, thus excluding blast crisis stage. Plentiful myelocytes, metamyelocytes and band cells were also seen. Basophilic precursors were seen more than the normal but were not in the range of accelerated phase. Erythropoiesis was suppressed because of markedly increased myelopoiesis but was normal with respect to sequence of maturation. That led to very high M:E ratio of 16:1. Megakaryocytic lineage showed mild hyperplasia. Active platelet formation was shown by morphologically normal megakaryocytes. Thus, aspiration picture was consistent with that of peripheral

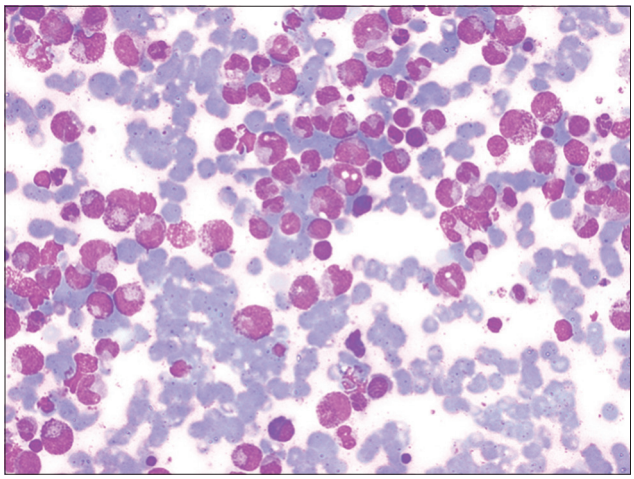

Figure 6: Leishman 40X BM aspiration in CML showing left shift of myeloid series showing promyelocyte, myelocyte, metamyelocyte, few blast cells, band form and mature neutrophils

blood smear and suggestive of Chronic Myeloid Leukaemia in chronic phase.

Chromosomes were analysed by karyotyping on total of 10 metaphases showing 46, XY, t(9q;22q). All metaphases showed positivity for Philadelphia chromosome (100%).

Minor Groove Binder Real Time RT-PCR assay, done for quantification of hybrid transcript showed that specimen contained 68.75% (high) 210 kDa protein of major BCR-ABL fusion transcript.

DISCUSSION

Cytogenetic hallmark of CML is Philadelphia (Ph) chromosome which was the first explicit chromosomal aberration associated with a human malignancy.[1] Reciprocal translocation occurs between chromosome 9 and chromosome 22 which leads to the formation of a fusion gene by juxta-positioning the Abl1 (Abelson, named after a leukaemia virus) gene on chromosome 9 (region q34) to a piece of the breakpoint cluster region (BCR) gene on chromosome 22 (region q11), which results in the production of a chimeric protein called BCRABL1.[6] BCR-ABL1 protein have constitutive kinase activity which play essential role in the pathogenesis of paediatric CML. Ph chromosome is identified in conventional cytogenetic, by FISH or by RT-qPCR methods.

The innate history of CML has been characterised into phases described as chronic phase (CP), accelerated phase (AP), and blast crisis (BC). European Leukaemia Net criteria for disease phase in CML are as follows:[7]

Chronic Phase: In CP, the peripheral blood shows leukocytosis (12-1000 X 10^9/L, median: ~80 X 10^9/L) due to neutrophils in various stages of maturation, with peaks in the proportions of myelocytes and segmented neutrophils; children often have higher WBC counts than adults (median: ~250 x 10^9/L), Significant granulocytic dysplasia is absent.[2] Blasts typically account for <2% of the WBCs. Absolute basophilia and eosinophilia are common. Absolute monocytosis may be present, but the proportion of monocytes is usually <3%, except in rare cases with the p190 BCR-ABL1 isoform, which often mimic chronic myelomonocytic leukaemia. Platelet counts are normal or increased to >1000 X 10^9/L; marked thrombocytopenia is uncommon in CP.[2] Nonspecific chief complaints like fever, night sweats, weakness, left upper quadrant discomfort, and bone pain. Most common physical findings are pallor, low-grade fever, ecchymoses, and hepatosplenomegaly. Splenomegaly is more common in patients with higher WBCs and in whom the platelets are lower.[8] Hyperleukocytosis and features suggestive of BM infiltration are seen with more advanced age.

Accelerated Phase: (1) a persistent or increasing high WBC count (>10 X 10^9/L) and/or persistent or increasing splenomegaly, unresponsive to therapy; (2) persistent thrombocytosis (> 1000 X 10^9/L), unresponsive to therapy; (3) persistent thrombocytopenia (<100 X 10^9/L), unrelated to therapy; (4) evidence of clonal cytogenetic evolution, defined by cells harbouring the Ph chromosome and additional cytogenetic changes; (5) >20% basophils in the peripheral blood; and (6) 10-19% blasts in the peripheral blood and/or bone marrow.[2]

CML-AP is less common in paediatric population. It is characterized by progressive symptoms such as fever, weight loss, night sweats, increased resistance to chemotherapy, high proportion of blasts (10%–20%), and increased basophilia.

Blast Crisis: The criteria for BP include (1) >20% blasts in the blood or bone marrow or (2) the presence of an extramedullary proliferation of blasts.[2]

Blast crisis phase in CML carries very poor prognosis with a median survival of only 3–9 months. It has features such as myeloid blastic (60%–70%), lymphoblastic (30%), or mixed lineage. Acute lymphoblastic leukaemia is more common among lymphoblastic pre-B cell leukaemia's.[9,10] Multi-lineage involvement is present which is responsible for cytological heterogeneity of the BC. The p53 mutation is obvious in late CP and may be a sign of increasing genomic volatility and premature succession to BC.[11,12]

Characteristics of paediatric CML compared to adult CML are as follows: (1) CML comprises 3% of paediatric leukaemia while adult CML 15%–20% of adult leukaemia. (2) CML-

CP is more common and CML-AP is less common.[13] The mean haematocrit in paediatrics at presentation is 25 ml/dl, which is remarkably less that seen in adults.[14,15] High median leukocyte counts (approximately 250,000/mm^3) and excessive hyper-leukocytosis (>500,000/mm^3) are more common.[13,16]

Pediatric CML comprises a small percentage of all leukemias and shares characteristics with adult CML.[17,18]

Margaret Lewen et al found that paediatric CML with inv(3)(q21q26.2) had more favourable treatment responses compared to adults.[19]

Hoho AN et al reported a case of paediatric CML which presented with normal leucocyte count with no immature cells in blood, patient only had extreme thrombocytosis with presence of BCR-ABL 1 fusion gene. This study highlights the importance of BCR- ABL 1 gene for diagnosing paediatric CML.[20]

CONCLUSION

As the study includes retrospective cases with very limited study population and could have included several biases, no confirmatory results could be drawn, however it may provide a preliminary but important information regarding the symptomatology and early age of affection of individuals in third world countries. Causes behind this early age of affection should be more thoroughly searched out which can definitely put light upon the etiopathogenesis of this one of the very important entity of haemato-lymphoid malignancy. Further work up can also be done on the molecular basis of the carcinogenesis which could help in disease management and prognosis establishment.

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Author's contribution:
KT-Concept and design of the study; prepared first draft of manuscript; **SI-**Concept, coordination, review of literature and manuscript preparation; **SA-**Interpreted the results; reviewed the literature and manuscript preparation; **NZ-**Statistically analyzed and interpreted, preparation of manuscript and revision of the manuscript; **ZF –** revision of manuscript.

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