REVIEW ARTICLE

Diagnosis and Treatment of Polycythemia Vera in Pakistan; Barriers and Possible Solutions

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Abstract

This review aims to highlight the challenges encountered in managing Polycythemia Vera in resource-limited settings and to suggest a cost-effective strategy for timely diagnosis and treatment. Presentation to healthcare facilities at an advanced stage due to lack of awareness and limited access to medical care, delay in the diagnosis due to inadequate healthcare infrastructure, unavailability of molecular testing in the majority of centers, and suboptimal disease management, primarily due to lack of physician awareness and expertise in handling this condition are the key factors contributing to the higher rates of complications, including thrombotic events and disease progression, ultimately leading to poorer patient prognoses in Pakistani population. This review describes and evaluates a cost-effective diagnostic and treatment approach to Polycythemia Vera to reduce the morbidity and mortality of the disorder in Pakistan. A tailored investigation plan comprising of JAK2 mutation and serum erythropoietin levels and minimal cytoreductive therapy combined with phlebotomy and anti-platelet agent can be implemented to achieve optimal management of the disease in a resource-constrained country.

Keywords: *Polycythemia Vera, Pakistan, cytoreduction therapy, cost effective, JAK2 mutation, erythropoietin levels.*

INTRODUCTION

Polycythemia Vera (PV) is a stem cell-derived clonal disorder that falls under the category of Philadelphia chromosome-negative myeloproliferative neoplasms, along with Essential Thrombocythemia and Primary Myelofibrosis. The prevalence of Polycythemia Vera is 1 out of 3,000 individuals, whereas the annual incidence worldwide is 1/100,000 persons/year. Sadia, et al, reported a similar prevalence of PV in Pakistan as in Western countries [1]. PV can occur in any age group but mostly affects older adults between the 5th and 7th decades of life [2]. There is a slight male preponderance with a 2:1 male-to-female ratio [3].

The pathogenesis of PV is exclusively driven by mutations in the exon 12 or 14 of the JAK2 gene, which encodes for the protein tyrosine kinase Janus kinase 2. The JAK2V617F mutation has been detected in 97% of cases of Polycythemia Vera [4, 5]. PV is primarily driven by the JAK2V617F mutation, which accelerates the risk of leukemic transformation. Advanced age, long disease duration, and somatic mutations in genes such as TP53, ASXL1, SRSF2, TET2, IDH1/2, and EZH2 mutations are additional contributing factors [6].

The cumulative risk of transformation into acute myeloid leukemia ranges from 2% to 15% over 10-20 years. In a large study, evaluating the outcomes of 1545 patients with PV, over a median follow-up of 7 years, post-diagnosis events included deaths (23%), leukemic transformation (3%), fibrotic progression (9%), arterial thrombosis (12%), venous thrombosis (9%) and major hemorrhage (4%). The most frequent causes of death in this study were leukemic transformation, second malignancies, and thrombotic complications [7].

The outcome of patients with PV in Pakistan is dismal owing to multiple factors. The mainstream of the population resides in suburban areas or countryside where individuals only have access to basic health care units, of which a large number are non-functional. The public sector hospitals in their vicinities do not offer adequate diagnostic services. They have limited access to tertiary care facilities, due to the large geographical distance, lack of infrastructure, and lack of proper transport. Another crucial factor is the lack of awareness regarding accurate investigations and treatment strategies which leads to an unnecessary delay in the diagnosis and referral to hematology experts at specialty-oriented centers [8].

There is a paucity of epidemiological data on PV published in Pakistan. Only a few single-center retrospective analyses of demographic characteristics and laboratory features have been published over the last several years. There are 2-3 studies available from Pakistan [9, 10].

The present review aims to focus on increasing the knowledge and understanding of the healthcare physicians in Pakistan by setting up a cost-effective diagnostic and treatment approach for PV so that the morbidity and mortality associated with the complications in PV can be curtailed and the quality of life and survival of patients with PV can be improved in Pakistan.

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Table 1: Updated diagnostic criteria by World Health Organization (2016) for Polycythemia Vera.

	Major Criteria	Minor Criteria
Hemoglobin or HCT	Men Hb >16.5g/dl or HCT >49% Women Hb>16.0g/dl or HCT >48% Or increased RCM	-
Bone marrow biopsy	Hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytuic proliferation with pleomorphic, mature, megakaryocytes (different in sizes)	-
JAK2V617F or JAK2 exon 12 mutation	Present	-
Erythropoietin levels	-	Subnormal
Criteria required for diagnosis included all 2 major or the first two major and the minor criterion		

Hb: hemoglobin; HCT: Hematocrit; RCM: red cell mass

Diagnosis

The World Health Organisation (WHO) criteria which was updated in 2016 are the foundation for diagnosing PV. It encompasses the evaluation of both laboratory and clinical features as shown in Table **1**.

The clinical diagnosis is almost always made in the polycythemic phase. According to data from southern Pakistan, Half of the patients seek medical treatment due to accidental abnormal findings. Although hyperviscosity in the microvasculature is linked to the most frequent first symptoms, such as headache, dizziness, blurred vision, paraesthesia, and erythromelalgia, thrombosis affecting large arteries or veins may be the presenting characteristic in a fraction of individuals. Gout, gastrointestinal bleeding, and unbearable itching are other symptoms. In 10-15% of people, some of these symptoms may manifest up to two years before an increase in hemoglobin or hematocrit levels is found [11].

The elevated erythrocyte count, hematocrit, and hemoglobin are the main findings in the peripheral blood. For the diagnosis, the hemoglobin level must be greater than 16.5 g/dL in men and greater than 16.0 g/dL in women. Nearly 50% of patients had thrombocytosis upon diagnosis, while over 60% of patients had leucocytosis. The diagnosis of PV can be established by getting the JAK2V617F mutation and serum erythropoietin levels on blood samples as per WHO criteria. Serum erythropoietin (EPO) level is expected to be less than normal in more than 85% of patients with JAK2 mutated PV. A normal or high Epo level raises the suspicion of secondary erythrocytosis which may result from defects in high-oxygen affinity hemoglobin variants, hypoxia-inducible factor mutations, cardio-pulmonary diseases, sleep apnea, or high-altitude living [12]. Patients with symptomatic hypogonadism on testosterone replacement therapy (TRT) tend to develop secondary polycythemia and venous thromboembolism, as testosterone directly increases hematocrit levels

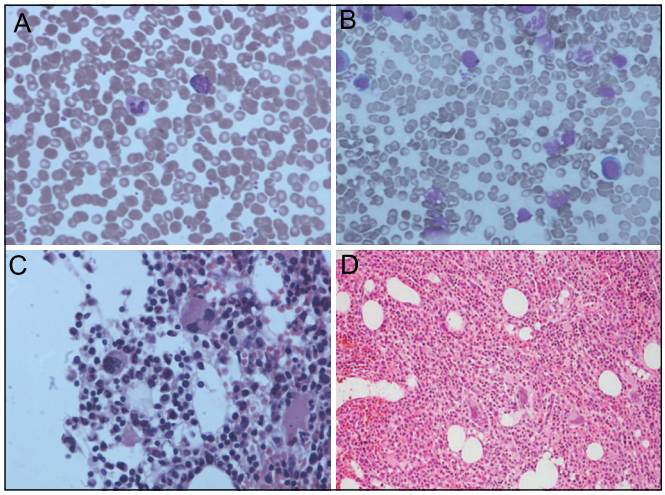

Fig. (1): Polycythemia Vera microscopic images. **(A)** Peripheral smear showing erythrocytosis. **(B)** Bone marrow aspirate showing characterize erythroid hyperplasia along with myeloid and megakaryocytic proliferation (Panmyelosis). **(C)** H & E section showing megakaryocyte pleomorphism. The cells are more easily evaluated by using the PAS staining reaction. **(D)** Reticulin stain showing MF grade 0-1 fibrosis.

[13]. Cigarette smoking contributes to polycythemia by impairing normal gas exchange and promoting carboxyhemoglobin formation, which reduces oxygen delivery to the kidneys, triggering erythropoietin release [14, 15].

The characteristic bone marrow findings of PV are best observed in trephine biopsy specimens as shown in Fig. **(1)**. The cellularity of the bone marrow ranges from 30 to 100% but is consistently hypercellular for the patient's age. Megakaryocytes are increased in number and they vary from small to large, may be dispersed singly throughout the bone marrow or form loose clusters, and are often located abnormally next to the bony trabeculae. Reticulin fiber content is normal in

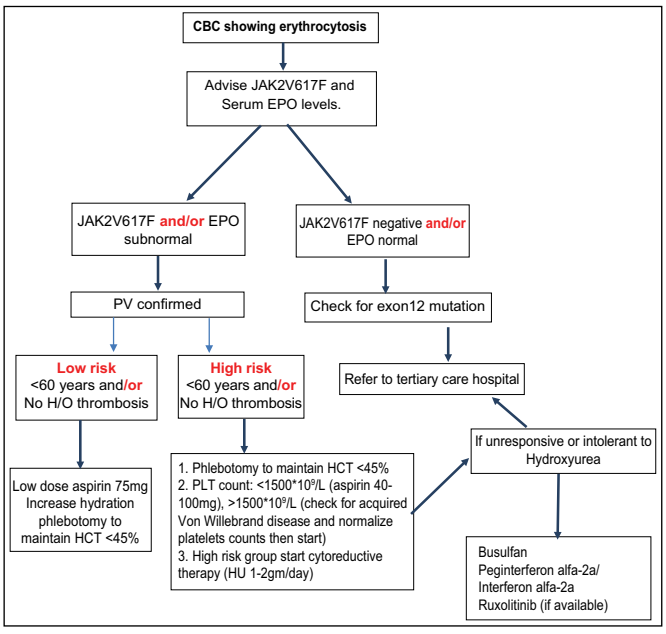

Fig. (2): Diagnostic & treatment algorithm for resource constrained settings.

most of the patients during diagnosis, but in as many as 20% of patients, reticulin fibrosis is noted even in the polycythemic phase. Stainable iron is absent in the aspirated marrow of more than 90% of patients [11].

Sadia *et al.* reported that the majority of Polycythemia Vera (PV) patients harbor the JAK2V617F (exon 14) mutation, with JAK2 exon 12 being the second most prevalent, involving multiple genes first identified in 2007 [1, 16, 17]. Akram *et al.* estimated that 5% of JAK2-negative PV cases carry exon 12 mutations [18]. Given that JAK2 mutations with subnormal erythropoietin (EPO) levels can confirm PV diagnosis, bone marrow biopsy is not essential at initial suspicion but may serve as a second-line investigation to assess cellularity, fibrosis, megakaryocyte morphology, and blast percentage [19, 20]. Ultimately reducing diagnostic costs and expediting referrals to tertiary care. The diagnostic algorithm for resource-constrained settings is shown in Fig. **(2)**.

Risk Stratification

Polycythemia Vera is known to be associated with substantial morbidity and reduction in the overall survival of the patients. Because of this, increasing attention is being paid to identifying various indicators of poor prognosis in PV, primarily focusing on age and the risk of thrombosis [21].

Conventional Risk Stratification

According to the current risk stratification system, individuals who are less than 60 years old with no prior history of thrombosis are considered low risk. All other patients are high-risk [6].

Risk Stratification for Thrombosis

Recent findings suggested that both PV and MF patients have a chance of developing venous and arterial thrombosis [22]. Cardiovascular risk factors, particularly hypertension and smoking may also contribute to an increased risk of thrombosis. Hypertension was associated with an increase in the annual incidence of thrombosis from 0.85% patients/year to 2.05% patients/year [23]. The results of the ECLAP study demonstrate that a leukocyte count >15 × 109 /L increased the risk of major thrombosis by 1.71-fold (95% CI, 1.1-2.6) compared with patients with ≤10 × 109 /L leukocytes [24]. It is estimated that, after the median 20-year follow-up in PV patients, the chances of thrombotic complications increased by 26% [7].

In Pakistan, the estimated risk of death due to cardiovascular disease in the general population is 30 to 40% and it is attributable to the increasing use of tobacco smoking and the sedentary lifestyle of young to middle-aged people which makes them vulnerable to thrombotic events [25].

A single-center study conducted in Karachi, Pakistan reported the occurrence of vascular events in 11.5% of PV patients and the most commonly observed event was a transient ischemic attack in 7.69% of patients [20].

Treatment of Polycythemia Vera

Until the last decade, the treatment of PV was chiefly intended to achieve a normal hematocrit level and to reduce the thromboembolic manifestations which are considered the leading cause of morbidity and mortality in PV [26, 27]. Regular phlebotomies along with aspirin to control the hematocrit remain the cornerstone of treatment. Keeping the hematocrit level below 45% significantly reduces the risk of death from cardiovascular causes. A randomized-controlled study was published by Marchioli and his colleagues in which 365 patients with PV received phlebotomies to maintain a target hematocrit of <45% or 45%-50%. Deaths due to thrombotic or cardiovascular reasons were reported in 2.7% (5/182) of patients in the group with <45% hematocrit as compared to 9.8% (18/183) patients in the group who maintained hematocrit between 45%- 50% [28].

Aspirin

In the large randomized ECLAP study involving 518 patients with polycythemia vera (PV), daily low-dose aspirin (100 mg) demonstrated significant efficacy and safety by reducing thrombotic events and mortality risk by 60% [29]. Low-dose aspirin should be cautiously used in patients with extreme thrombocytosis (platelet count >1000 × 109/L), which promotes the development of acquired Von Willibrand syndrome [28].

Busulfan

Busulfan is a potent alkylating agent that inhibits the cell cycle. It has been used previously in patients refractory and intolerant to first and second-line therapies. Kuriakose *et al.* have shown that busulfan was administered to six patients who had refractory PV, and complete hematological response was achieved within three months in all the patients while their median duration of therapy was 56.5 months [30]. Reported adverse effects include thrombocytopenia with an increased risk of leukemic transformation. A prospective observational analysis of 1638 patients from the ECLAP study assessed the risk factors for AML/MDS in PV patients. Exposure to P32, busulphan, and pipobroman (HR, 5.46; 95% CI, 1.84-16.25; P = .0023), but not to hydroxyurea alone (HR, 0.86; 95% CI, 0.26-2.88; P = .8021), demonstrated an increased risk of progression to AML/MDS [31].

Hydroxyurea/Hydroxycarbamide

Hydroxyurea is an antimetabolite drug that inhibits DNA synthesis, and it has been traditionally used for cytoreduction in high-risk PV patients [32]. Hydroxyurea is initiated at a dose of 1000-2000 mg/day, with dose escalation recommended if platelet levels remain within the normal range [33]. Compared to therapeutic phlebotomy, it lowers the occurrence of thrombotic events. Several studies have confirmed the low incidence of AML in PV patients treated with hydroxyurea (1%-5.6%) [31]. A subset of patients experience intolerance

Table 2: Studies outcome of PV investigational drugs with their toxicities in JAK2V617F positive Polycythemia patients.

Reference	Study Type	Dose	Trial Outcome	Toxicities
GIVINOSTAT				
Rambaldi, A.; *et al.* [25]	Cohort	50 mg daily	01 patient shows CHR 06 patients shows PHR 07 became phlebotomy independent	No grade 04 toxicity
Finazzi, G.; *et al.* [26]	Randomized phase II study	Hydroxyurea (MTD)+ginivostat 50 mg OD/BD	CHR: 55% PHR 50%	Grade 3 AE in 4.5% of cases
Rambaldi, A.; Iurlo, A.; *et al.* [27]	Randomized phase Ib/II	Givinostat 100mg BD (04 weeks)	ORR: 86.6% improvement in JAK2V617F allele burden	Grade 3 AE
IDASANUTLIN				
Mascarenhas, J.; *et al.* [28]	Phase I clinical study	100 mg and 150 mg OD 5 days(28 days cycle), total 06 cycles	ORR: 75% Median duration of response: 16.8 months	Grade 3 non-hematologic AEs (41.7%), grade 1/2 nausea (83%)

CHR: complete hematological response
PHR: partial hematological response
ORR: overall response rate
AE: Adverse events

to hydroxyurea due to its undesirable effects like mucocutaneous ulcers and myelosuppression [34]. Therefore, hydroxyurea is reported as the most common treatment modality with fewer ADRs and good tolerance.

Interferon

Interferon-alpha has shown promising results concerning hematocrit control and reduction in spleen size in PV as well as relieving constitutional symptoms like pruritis and erythromelalgia. In an initial study of pegylated interferon alpha, 70% of patients with PV achieved complete hematological remission within the first 3 months of treatment [35]. Moreover, ropeginterferon, which is a newer form of pegylated interferon, has been shown to induce high responses with minimal toxicity and better tolerance in PV patients [36]. Unlike conventional therapies, this is one of the few disease-modifying treatments with the potential to reduce the JAK2V617F allele burden [37]. A randomized controlled trial to prove the efficacy and advantages of interferon therapy in high-risk PV patients is still ongoing [37]. Studies with newer agents in the management of PV are shown in Table **2**.

Ruxolitinib

Ruxolitinib is the only JAK1/JAK2 inhibitor that has been approved by the FDA for high-risk PV cases resistant or intolerant to hydroxyurea based on the results of a phase III clinical trial [38]. Vannucchi *et al.* demonstrated that ruxolitinib provided superior hematocrit control, symptomatic relief, and spleen reduction compared to standard therapy; however, its impact on overall outcomes, leukemic progression, and thrombo-hemorrhagic events remained unevaluated in this study [39]. The impact of Ruxolitinib on thrombotic events has been reported to be lower than hydroxyurea in a recent meta-analysis that considered four randomized controlled trials, including 663 patients, but this difference was not statistically significant ($p = 0.098$) [40].

Strategies and Recommendations to Overcome Treatment Limitations in Polycythemia

Healthcare in Pakistan, particularly in socio-economically deprived regions, faces significant challenges. Prompt diagnosis of lethal disorders is crucial to avoid scenarios where the only option left is palliative care. This is particularly evident in the case of Polycythemia Vera (PV), a myeloproliferative disorder that often goes undiagnosed until it reaches a high-risk stage due to delayed presentation, lack of diagnostic facilities, and inadequate referral systems.

Diagnostic Challenges and Solutions

In Pakistan, a significant proportion of PV patients present with high-risk disease at the time of diagnosis. This delay can be attributed to several factors, including limited access to diagnostic facilities and insufficient awareness among general physicians regarding the disorder. To address these issues, several private sector laboratories have expanded their services by establishing collection points and offering home-phlebotomy services in the outskirts of cities and smaller districts within Sindh, Baluchistan, and Punjab provinces. These advancements can significantly aid general physicians by enabling them to order essential tests like the JAK2 mutation and serum erythropoietin levels, thus facilitating the timely diagnosis of PV.

The establishment of these collection points and mobile phlebotomy units represents a crucial step forward. By bridging the gap between remote populations and diagnostic facilities, these services can ensure that more patients receive a diagnosis before their condition worsens. This proactive approach not only enhances the chances of effective management but also reduces the burden on tertiary care centers by managing conditions at an earlier stage.

Treatment Goals and Primary Care Solutions

The primary treatment goals for PV are to normalize hematocrit levels and minimize the risk of thrombo-hemorrhagic events. Phlebotomy is the first line and standard of care for PV treatment and can be performed in basic healthcare units by trained phlebotomists. These professionals need adequate training to understand the volume to be depleted and the necessity of fluid

replacement. By equipping basic health units with trained phlebotomists, the healthcare system can ensure that initial PV management is accessible even in resource-limited settings.

Additionally, low-dose aspirin, which helps reduce the risk of cardiovascular complications, is readily available and can be initiated alongside phlebotomies in patients presenting with high hemoglobin and hematocrit levels. Hydroxyurea, the preferred cytoreductive agent for high-risk PV, is also widely available and affordable in Pakistan, contributing to better patient compliance. The treatment algorithm for resource-constrained settings is shown in Fig. **(2)**.

Advanced Treatment Options and Accessibility

For patients who do not respond to initial therapies, advanced treatments like the JAK2 inhibitor, ruxolitinib, are now available at tertiary care centers across major provinces at a subsidized cost, thanks to patient access programs by pharmaceutical companies. This drug offers a crucial alternative for patients who require more aggressive management.

Interferon alpha, another treatment option, is available at select centers in Karachi and Lahore. When used on a fortnightly or monthly basis, it proves to be a cost-effective treatment, making it accessible for patients from various socio-economic backgrounds.

Educational Initiatives and Professional Development

To enhance the understanding and management of PV among healthcare professionals, several academic activities and workshops have been organized over the past 7-8 years by institutions such as the National Institute of Blood Diseases & Bone Marrow Transplantation (NIBD & BMT). These educational initiatives aim to train physicians, hematologists, and laboratory personnel on how to suspect PV in patients presenting with erythrocytosis, as well as how to conduct appropriate investigations and provide initial treatment until patients can be referred to a specialized hematology center.

An important development in this regard is the establishment of the Myeloproliferative Neoplasm (MPN) expert forum. This platform allows hematologists and physicians to share their experiences and enhance their knowledge about PV and related disorders. Such forums foster a collaborative approach to managing PV, ensuring that best practices are disseminated and implemented across the country.

Comprehensive Algorithm for Diagnosis and Treatment

To further streamline the diagnosis and treatment process in resource-limited settings, a comprehensive algorithm has been developed as shown in Fig. **(3)**. This algorithm provides clear guidelines for general physicians on the steps to take when PV is suspected.

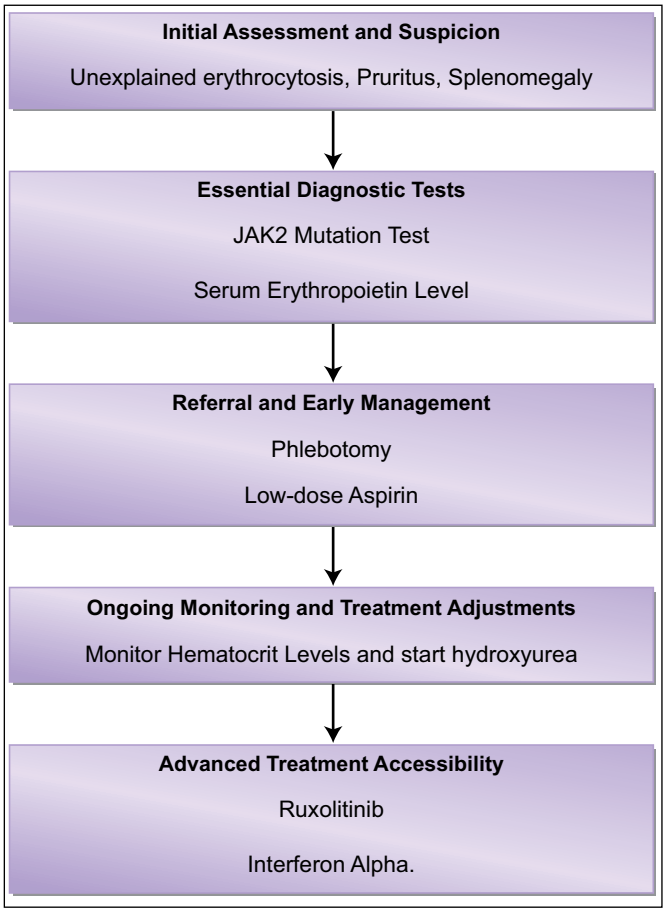

Fig. (3): Polycythemia Vera (PV) management protocol for general physicians.

CONCLUSION

The healthcare system in Pakistan faces significant challenges in diagnosing and managing PV, particularly in socio-economically deprived regions. However, by enhancing diagnostic accessibility, training healthcare professionals, and establishing comprehensive treatment algorithms, these challenges can be mitigated. The expansion of diagnostic facilities through collection points and home-phlebotomy services, combined with the availability of essential medications like hydroxyurea and advanced treatments such as ruxolitinib and interferon alpha, provides a robust framework for managing PV.

Furthermore, ongoing educational initiatives and the establishment of expert forums play a crucial role in fostering a knowledgeable and collaborative healthcare environment. These efforts ensure that best practices are shared and implemented, ultimately improving patient outcomes.

As Pakistan continues to develop its healthcare infrastructure, it is essential to maintain a focus on these strategic areas. By prioritizing early diagnosis, accessible treatment, and continuous professional development, the healthcare system can effectively address the limitations currently faced and improve the prognosis for patients with PV and other similar disorders.

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CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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AUTHORS' CONTRIBUTION

RJ: conducted the literature review, and drafted the manuscript.

SMK: contributed to data synthesis, manuscript revision, and critical analysis.

GS: conducted the literature review

SNM: conducted the literature review

UZ: provided supervision, final review, and approval of the manuscript.

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