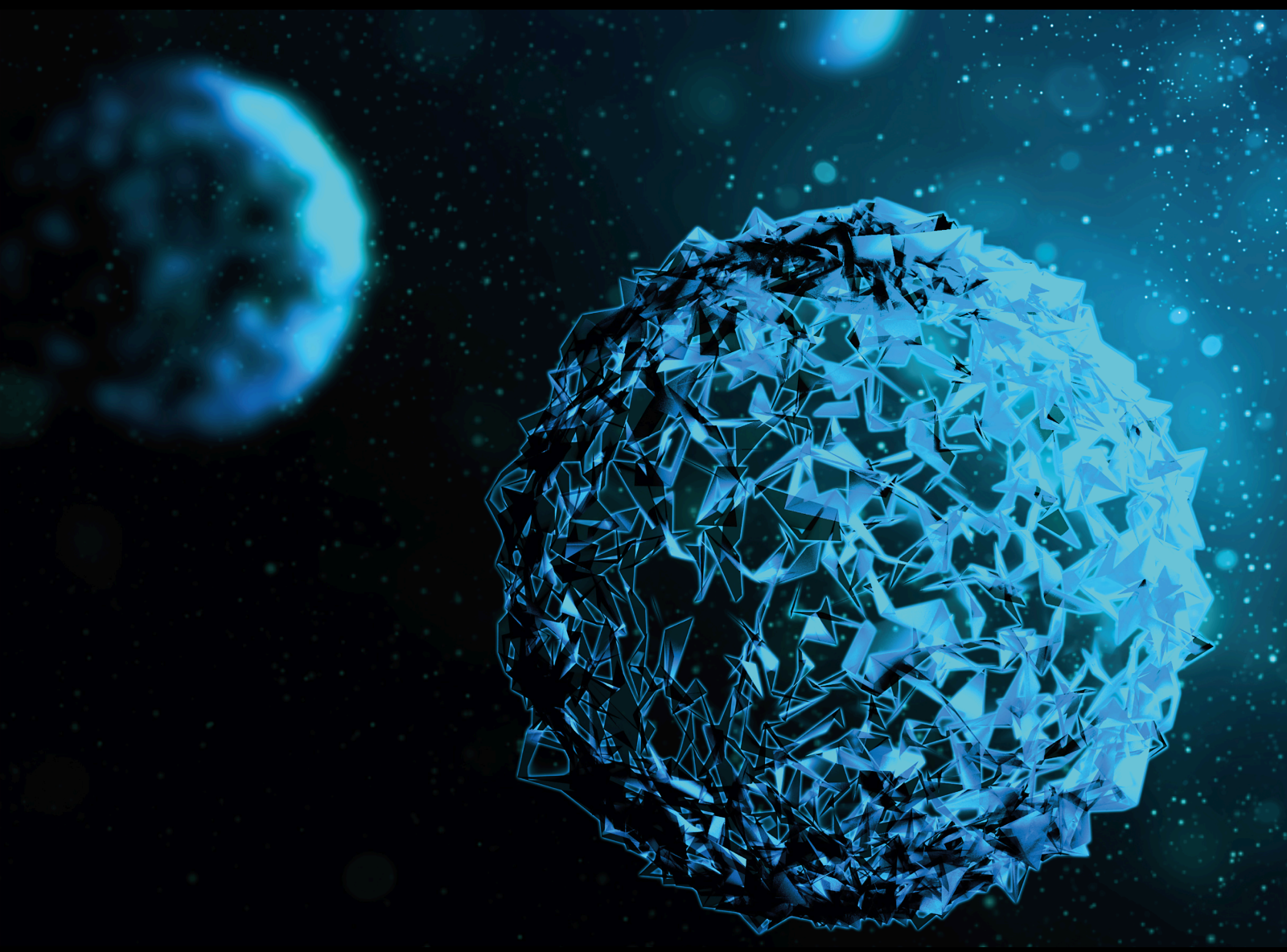
BioMed Research International

Value-Based Medical Care and Cost-Effectiveness Principles Dissemination across Emerging Markets

Lead Guest Editor: Mihajlo Jakovljevic
Guest Editors: Tissa Wijeratne and Maria José Muñoz Torrecillas



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Corrigendum

Corrigendum to "Utilisation Trend of Long-Acting Insulin Analogues including Biosimilars across Europe: Findings and Implications"

Brian Godman,[1,2,3] Magdalene Wladysiuk,[4,5] Stuart McTaggart,[6] Amanj Kurdi,[1,2,7] Eleonora Allocati,[8] Mihajlo Jakovljevic,[9,10,11] Francis Kalemeera,[12] Iris Hoxha,[13] Anna Nachtnebel,[14] Robert Sauermann,[14] Manfred Hinteregger,[14] Vanda Marković-Peković,[15] Biljana Tubic,[16,17] Guenka Petrova,[18] Konstantin Tachkov,[18] Juraj Slabý,[19] Radka Nejezchlebova,[19] Iva Selke Krulichová,[20] Ott Laius,[21] Gisbert Selke,[22] Irene Langner,[22] András Harsanyi,[23] András Inotai,[24] Arianit Jakupi,[25] Svens Henkuzens,[26] Kristina Garuolienė,[27] Jolanta Gulbinovič,[27] Patricia Vella Bonanno,[1,28] Jakub Rutkowski,[5] Skule Ingeberg,[29] Øyvind Melien,[29] Ileana Mardare,[30] Jurij Fürst,[31] Sean MacBride-Stewart,[32] Carol Holmes,[33] Caridad Pontes,[34,35] Corinne Zara,[34] Marta Turu Pedrola,[34] Mikael Hoffmann,[36] Vasileios Kourafalos,[37] Alice Pisana,[38] Rita Banzi,[8] Stephen Campbell,[39,40] and Bjorn Wettermark[41]

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In the article titled "Utilisation Trend of Long-Acting Insulin Analogues including Biosimilars across Europe: Findings and Implications" [1], the captions of Figures 3 and 4 were incorrect. The corrected captions for Figures 3 and 4 appear below.

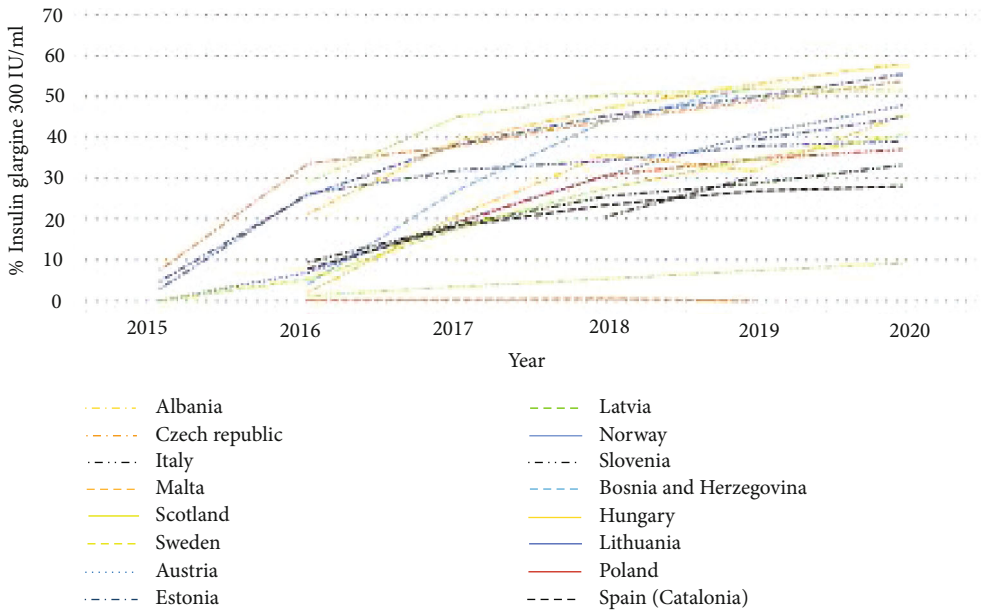

Figure 3: Utilisation of insulin glargine 300 IU/ml (Gla-300) as a % of total insulin glargine (DDD based) across Europe over time.

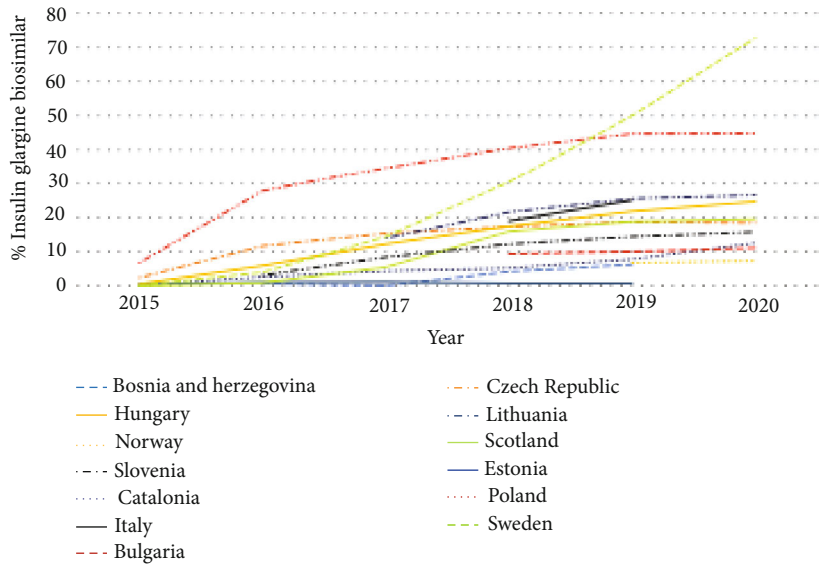

Figure 4: Utilisation of insulin glargine biosimilar (100 IU/ml) as a % of total insulin glargine 100 IU/ml (DDD based) over time across Europe.

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[1] B. Godman, M. Wladysiuk, S. McTaggart et al., "Utilisation Trend of Long-Acting Insulin Analogues including Biosimilars across Europe: Findings and Implications," *BioMed Research International*, vol. 2021, Article ID 9996193, 16 pages, 2021.

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Review Article

Systematic Review of Existing Stroke Guidelines: Case for a Change

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Background and Purpose. Stroke represents one of the most important causes of morbidity (Just over hundred million patients with disabling of ongoing effects of stroke at a given time, globally) and mortality (the second leading cause of death) worldwide. Innovative system biology-based approach is likely to increase the understanding of the underpinning of acute stroke promise to enhance stroke prevention, acute treatment, and neurorehabilitation. Recent growing body of evidence with shared pathobiology with COVID-19 and the critically important role of inflammation in the context of stroke points to far-reaching consequences of acute stroke, just as in the case of COVID-19 (postacute event issues as well as long term issues). So far, stroke is typically defined by late-appearing disease manifestation by the range of stroke subtypes as defined by the WHO or American Stroke Association. This definition neglects the underlying pathobiological mechanisms such as low-grade chronic inflammation and already compromised vascular system. Diseases such as stroke are hardly a simple result of a single problem but rather a complex cascade of pathobiological processes and interactions in a complex biochemical environment. The evidence of changes in innate immunity and adaptive immunity during the index event of acute stroke and recovery over next 3-12 months can be easily elicited with simple bedside blood tests such as neutrophil-lymphocyte ratio (NLR) with well over 300 published papers including several systematic reviews and meta-analyses confirming this. Global standard operating procedures (SOP) of stroke care are dictated by the national and international stroke guidelines at present. It is imperative to explore the evidence of system biology approach in current stroke guidelines. This is likely to be a key turning point in managing stroke across the continuum (prevention, management of acute event, and rehabilitation). *Methods.* We systematically searched for guideline recommendation on the day-to-day use of peripheral inflammatory markers such as NLR published in the English language between January 1, 2005, and October 2020. Any other evidence of system biology-based approach or recommendation was explored within the selected guidelines for this scoping review. Only the latest guideline per writing group was selected. Each guideline was analyzed independently by 2 to 4 authors to determine clinical scenarios explained/given, scientific evidence used, and recommendations presented in the context of system biology. *Results.* The scoping review found 2,911 titles at the beginning of the search. Final review included with 15 guidelines. Stroke-related organizations wrote sixty-five percent of the guidelines while national ministries wrote a fewer number of guidelines. We were primarily interested in recommendations for acute management in AIS published in the English language. Fifteen eligible guidelines were identified from 15 different countries/regions. None of the guidelines recommended the routine use of

peripheral markers of inflammation, such as NLR, among their acute assessment and management recommendations. None of the existing guidelines explored the system biology approach to one of the most complex diseases affecting the human brain, stroke. *Conclusions.* This systematic review has identified a significant evidence-practice gap in all existing national stroke guidelines published in English medium as of October 2020. These guidelines included the only current "living stroke guidelines," stroke guidelines from Australia with a real opportunity to modernize the living stroke guidelines with systems biology approach, and provide 2020 vision towards better stroke care globally. Investigation of complex disease such as stroke is best served through a systems biology approach. One of the easiest places to start is simple blood tests such as total white cell count and NLR. Systems biology approach point us towards simple tools such immune-inflammatory index (SII) and serial systemic immune inflammatory indices (SSIIi) which should pave the way for the stroke physician community address the challenges in systems biology approach in stroke care. These challenges include translating bench research to the bedside, managing big data (continuous pulse, blood pressure, sleep, oxygen saturation, progressive changes in NLR, SII, SSIIi, etc.). Working with an interdisciplinary team also provides a distinct advantage. Recent adoption of historic WHO-IGAP calls for immediate action. The 2022 World Brain Day campaign on Brain Health for All is the perfect opportunity to raise awareness and start the process.

1. Introduction

Evidence-based medicine calls for the utilization of widely available clinical guidelines especially for the management of common conditions which have an impact on mortality and morbidity such as acute ischemic stroke (AIS). The first of this kind was published in 1974 which was entitled "Prologue to Guidelines for Stroke Care," a compendium of articles compiled by neurologists on the management of cerebrovascular disease [1] It was not until more than 20 years later that the Cochrane Collaboration Stroke Review Group convened and initiated the task of constructing a systematic guideline for the management of acute stroke [2].

Clinical guidelines are essential tools to improve the quality of healthcare systems. Factors which are crucial for a clinical guideline to be successfully crafted are team collaboration and multidisciplinary engagement [3, 4]. Furthermore, these should be tailor-fitted to individual country needs, hence, the nonexistence of a universally implemented guideline [4]. The use of tools to assess the quality of evidence also aids clinicians to interpret the recommendations according to the weight of evidence [5]. Potential barriers to nonadherence include unfamiliarity, lack of agreement, and outcome expectancy, as well as the significant impact of the precedent guideline [6].

Perhaps one of the game changers in the history of medicine is the development of clinical guidelines for the management of AIS. The wealth of data from clinical trials on reperfusion therapies paved the way for the American Heart Association (AHA) and the Canadian Stroke Consortium to publish their respective recommendations on the acute intervention of cerebrovascular ischemia [7, 8]. Through time, various versions of clinical guidelines have also been published in different languages with the primary objective of implement ability according to the resources available in each country. While constructs behind these standard procedures are anchored on the same theory, some degree of variability still occurs [9]. To date, there are no studies which specifically look at the differences in the clinical guidelines on acute ischemic stroke globally. It is in this light that this study was conceived.

2. Methodology

The authors of this review used the Arksey and O'Malley methodology to identify and extract useful literature. The steps undertaken include (1) research question identification; (2) relevant literature identification; (3) screening and selection of relevant literature; (4) data charting; and (5) analyzing, summarizing, and reporting results.

MEDLINE, Cochrane, and CINHAL databases were searched to identify useful keywords. Subsequently, the identified keywords were used to search the same databases for relevant studies. Literature were first screened at the title and the abstract level and then the full text articles.

Following search terms were employed based on the PICO strategy. Topic = "country name" AND TOPIC = "guideline" OR" clinical protocols" OR "recommendations" OR" standards" AND TOPIC = stroke OR cerebrovascular disorder OR cerebrovascular accident.

Guideline repositories such as the National Guideline Clearinghouse, the Scottish Intercollegiate Guidelines Network (SIGN), and Professional stroke societies were also searched. Individual bibliographies were also manually searched. Studies were included if they met the following criteria: (a) published after year 2000, (b) guidelines on stroke and/or poststroke rehabilitation, (c) graded recommendations, and (d) written in English. Titles and abstracts were initially screened (TW), and any full-text articles were further appraised (TW, CS). Any disagreement was adjudicated by an independent reviewer (LK). Guidelines which were updated in a modular format and published over separate papers were treated as one guideline.

3. Results

3.1. Guideline Characteristics. Figure 1 shows the diagram on available stroke guidelines worldwide. Figure 2 shows the PRISMA diagram of the process. Majority of the countries have no available published national guidelines while a number have guidelines but no graded recommendations. A significant majority also have guidelines published in their own language while 14 countries have their own published, graded, English clinical guidelines, with the one from the European Stroke Organization as a separate entity.

A total of 2897 titles were identified in the electronic search. Fourteen additional records were identified through other sources. After removal of duplicates and screening at the title level, 255 articles were further reviewed at the abstract level. Hundred and eighty-one papers were

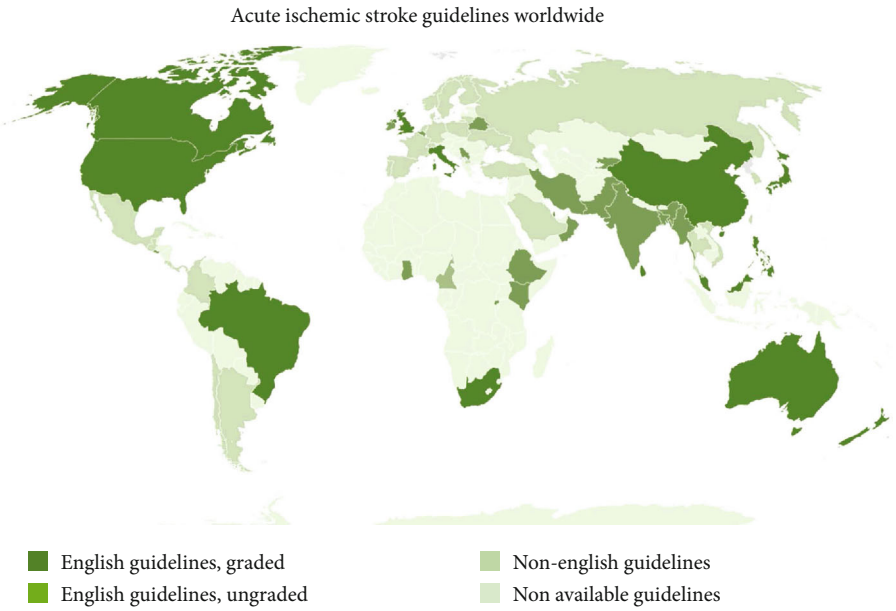

Figure 1: Acute ischemic stroke guidelines worldwide.

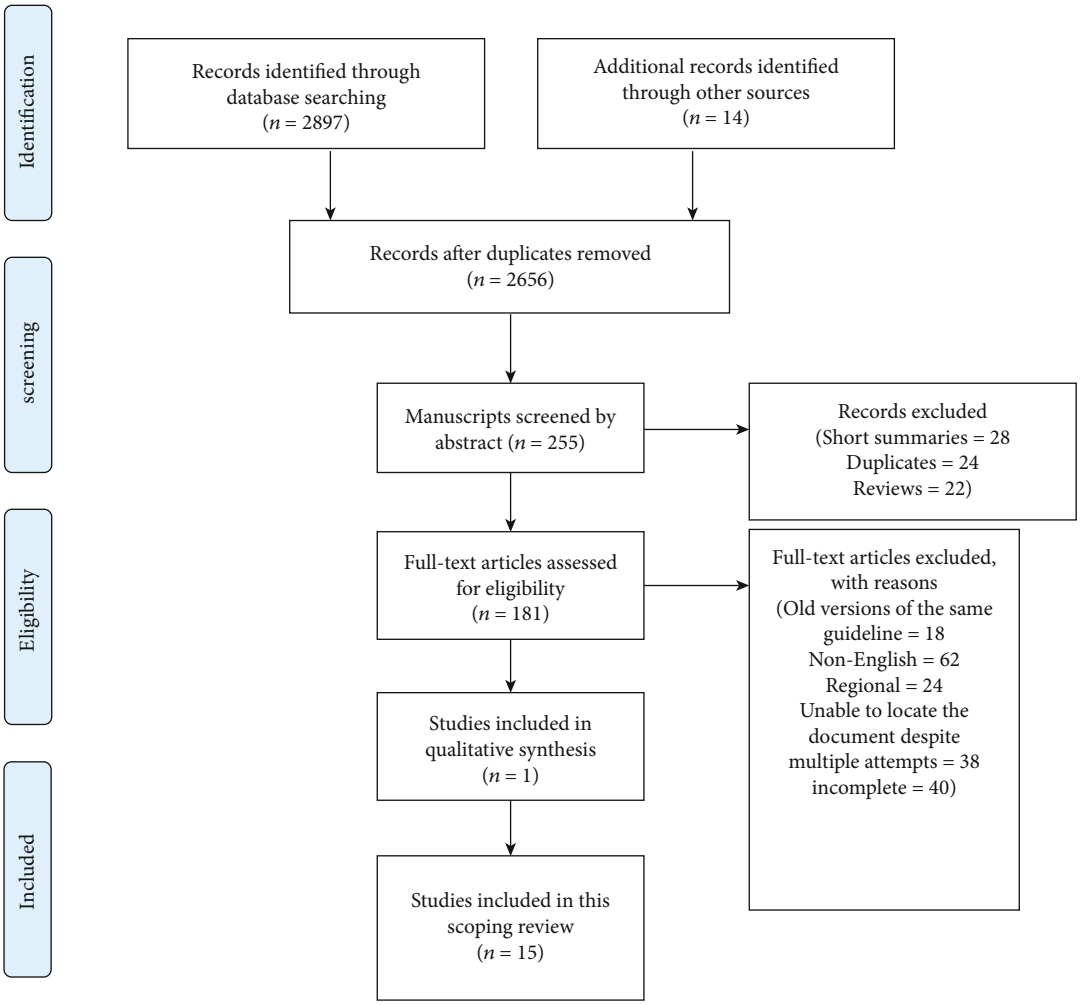

Figure 2: PRISMA diagram.

Table 1: Summary of acute ischemic stroke clinical guidelines.

Country	Name of guideline	Year of first published version	Subsequent revisions
Australia/New Zealand [10]	Clinical Guidelines for Stroke Management	2007	2010, 2019
Brazil [11]	Guidelines for Acute Ischemic Stroke Treatment	2001	2012
Canada [12]	Canadian Best Practice Recommendations for Acute Stroke Management	1998	2006, 2008, 2010, 2015, 2018
China [13]	The Chinese Stroke Association scientific statement: intravenous thrombolysis in acute ischemic stroke	2012	2014, 2017
ESO [14]	European Stroke Organisation–Karolinska Stroke Update	2003	2015, 2017, 2019
Italy [15]	The Italian guidelines for stroke prevention	2000	
Japan [16]	Japanese Guidelines for the Management of Stroke	2004	2009
Malaysia [17]	Clinical practice guidelines, management of ischemic stroke	2003	2006
Qatar [18]	Clinical Guidelines for the State of Qatar, the Diagnosis and Management of Stroke and TIA	2016	
Scotland [19]	Management of patients with stroke and TIA: assessment, investigation, immediate management, and secondary prevention	2008	
Singapore [20]	Stroke and TIA: assessment, investigation, immediate management, and secondary prevention	2009	2011
South Africa [21]	South African guideline for management of ischemic stroke and transientischemic attack 2010: a guideline from the South African Stroke Society (SASS) and the SASS Writing Committee	2000	2010
Sri Lanka [22]	Clinical practice guidelines, management of stroke	2017	
UK [23]	National clinical guideline for stroke	2000	2016, 2017
USA [24]	Guidelines for the early Management of Patients with Acute Ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke	1994	1996, 2003, 2005, 2007, 2013, 2015, 2018/2019

thoroughly assessed by the two authors (TW and CS) for eligibility. A total of 15 guidelines were included in this scoping review.

Table 1 outlines the characteristics of the 15 clinical guidelines included in this study.

3.2. Regionalization and Adaptation from Other Clinical Guidelines. Most countries worldwide have no available published national guidelines. However, this does not translate to lack of systematic processes and workflows in the management of acute ischemic stroke. The European Stroke Organization has successfully implemented the ESO Stroke Guidelines which is being operationalized by countries in the European region [14]. A unified approach is also being implemented in Australia and New Zealand as they both adapt the Australian Clinical Guideline for Stroke Management published in 2017 [25]. More recently, the Middle East and North Africa Stroke and Interventional Neurotherapies Organization has also created a consolidated plan to manage stroke in the midst of the pandemic [26].

Most of the conceptualized guidelines have been adapted from existing ones, usually from high-income countries [27]. A systematic review comparing stroke clinical practice guidelines (CPGs) from low- and high-income countries revealed a degree of compromise in terms of the quality on the former [27]. It is in this reason that in 2014, the World Stroke Organization conceived the *WSO Global Stroke Services Guideline and Action Plan* [28]. This initiative aims to aid country-level health authorities to set up or improve existing stroke frameworks to achieve high-quality, evidence-based recommendations and ensure that outcomes are measured to foster a milieu for continuous improvement [27].

3.3. The Need for Grading Recommendations. While countries have their own specific treatment recommendations, grading of evidence with the use of standardized systems is lacking. It is essential for guidelines to incorporate these as it ensures transparency and some level of confidence as these recommendations are translated into clinical practice [29]. Various country-specific guidelines make use of their own grading systems in assessing the weight and level of evidence of the recommended guidelines [12, 14, 24]. It is also essential for grading systems to be customized accordingly for low-income countries. Epidemiologists suggest the adaptation of internationally recognized approaches with efforts to integrate local evidence and weigh in appropriate resources [30].

3.4. Clinical Trials That Changed the Guidelines. In 1994, the AHA published the first clinical guideline on the management of acute ischemic stroke [31]. While the efficacy of

thrombolytic therapy was already being recognized then, it remained to be in the sidelines for safety concerns [31, 32]. With the encouraging results of the NINDs trial and the subsequent approval of alteplase by the US-FDA for systemic reperfusion, the AHA guidelines were updated, and it was also within this period that the Canadian Stroke Guidelines were conceived [7, 8, 33]. Other major clinical guidelines from different parts of the world were also published subsequently.

With the aim of further improving stroke care, further modifications of then existing guidelines have been made. With the promising results of the ECASS3 trial, the time period for thrombolysis has been extended from three to 4.5 hours [34, 35]. The results of the J-ACT trial in 2006 has also resulted in the approval for use of the 0.6 mg/kg dose of alteplase as mandated by the revised 2009 Japanese guidelines for stroke [16, 36].

The results of five clinical trials on endovascular therapy from 2012 to 2014 have also revolutionized the landscape of stroke management in the year 2015. The MR CLEAN, ESCAPE, EXTEND-IA, SWIFT-PRIME, and the REVASCAT trials showed statistically significant improvement in clinical and radiologic outcomes after endovascular therapy (EVT) for large vessel occlusion [37–41]. Clinical guidelines were revised so that patients within six hours from onset of symptoms were deemed eligible for EVT [10, 12, 24]. A few years later, this time period was extended to 16-24 hours based on perfusion imaging parameters, as demonstrated by the DAWN and the DEFUSE 3 trials [42, 43]. Various clinical trials are still in the pipeline and are expected to make significant changes in existing guidelines worldwide in the future.

3.5. Initial Assessment. Guidelines included in the study are represented from all parts of the world including Asia, Australia, Europe, Africa, and America (Table 1). Sections of clinical guidelines are subdivided into initial assessment, supportive treatment, reperfusion therapy, management of complications, and rehabilitation. In most guidelines, prehospital and preventive strategies are usually included, but these are not discussed in this study. It is noted that some degree of variability in grading exists with the appraisal of different clinical guidelines.

In terms of initial assessment, there is unanimity in the clinical strategies that all patients suspected to have stroke should have neuroimaging urgently. This received the strongest recommendation among most of the countries with only ones from USA and Qatar, putting significant weight on aiming less than 20 minutes for it to be accomplished. High-income countries who have established facilities for endovascular thrombectomy also put the priority on neurovascular imaging. On the other hand, only a number of countries emphasize the use of scales for stroke severity assessment.

The importance of neuroimaging cannot be overemphasized in the management of acute stroke. While seamless processes to ensure efficiency in initial brain scanning have already been established in high-income countries, limitations in resources and logistics are still problematic most especially in rural areas of low to middle-income countries [44]. For example, a tertiary center in India identified that the lack of neuroimaging facilities posed as one of the most important barriers for thrombolysis, with even the out of pocket cost for CT scan contributing to this limitation [45]. It is also practical for other countries such as Sri Lanka, South Africa, and Malaysia not to put too much weight on neurovascular imaging as inaccessibility to neurointerventionists and comprehensive stroke centers, as well as the high cost of treatment for this sophisticated procedure, is still one of the identified problems in most developing countries [46]. On the other hand, among countries in which reputable standard operating procedures for neuroimaging are already existent, aiming to shorter door to imaging times are being optimized, as trends to improved clinical outcomes have been observed [47].

There is also homogeneity among different countries in terms of what ancillary tests are to be performed during the hyperacute management of stroke. Serum blood glucose is being specified as an absolute test to be done prior to thrombolysis in some countries while in some, this is not explicitly identified. There is also unanimity among different countries that troponin, immune cell counts, and ECG should not be deterrents to timely thrombolysis. While obtaining baseline temperature is deemed significant in almost all clinical guidelines, less degree of weight is put in this parameter as opposed to blood glucose.

It has long been recognized that hypo and hyperglycemia are known stroke masquerades [48]. A study in 2015 among 80 consecutively recruited hypoglycemic patients revealed that 11% had stroke-like presentation with symptoms reversing within one hour of administration of intravenous dextrose [49]. Furthermore, it is also essential that this parameter be recognized and corrected at an early stage as glycemic aberrations in the perithrombolysis period may significantly impact on clinical outcomes [50]. While deemed equally important, cardiac investigations should not preclude nor delay thrombolysis. It has been demonstrated in various studies that the presence of strain pattern, *t*-wave alterations, and QT dispersion may be predictors of poor outcomes among stroke patients [51–53]. Troponin is also essential to exclude the co-occurrence of AIS and acute myocardial infarction. A national registry including more than 800,000 patients with AIS identified that simultaneous occurrence of both only happens in 1.6% of the patients [54]. While the incidence is significantly low, substantial increase in hospital mortality has been observed [54].

3.6. General Supportive Care. There is heterogeneity in terms of supportive care among acute stroke patients with most clinical guidelines stressing moderate to strong recommendations on airway protection, correction of fluid imbalances, and treatment of sources of hyperthermia and hypoglycemia. Consensus for blood pressure targets is not uniform, with Caucasian guidelines emphasizing a threshold of 180/105 prior to thrombolysis while some Asian guidelines follow a higher target [17, 20].

It is essential that acute stroke units be organized in a manner that caters to the efficient provision of

abovementioned parameters as this has been positively associated with good outcomes such as reduction of mortality, length, and cost of hospitalization as well as institutionalization [55, 56]. This is particularly problematic in low- to middle-income countries because of concerns for costs, facilities, and hospital staffing. Contrary to this, a recent prospective observational study in a tertiary hospital in South Africa demonstrated that despite the resource limitations, adaptation of the acute stroke response network which integrates organization of an acute stroke unit yields favorable thrombolysis outcomes at par to those observed in developed countries [57, 58].

Evidence proves that blood pressure optimization during thrombolysis results in good functional outcomes [59]. Prospective and retrospective studies as well as clinical trials reveal that blood pressure during thrombolysis ranging from 140 to 160 reduced the odds of poor outcomes [60–62]. To date, no studies have identified the most optimal blood pressure to achieve best outcomes post reperfusion therapy; however, clinical trial targets are set at 180/105; hence, the parameters are set in clinical guidelines [24].

3.7. Thrombolysis and the Management of Medical and Surgical Complications. There is also agreement between different guidelines that thrombolytic therapy (tissue plasminogen activator, alteplase) at a dose of 0.9 mg/kg be instituted among eligible patients who arrive between three and 4.5 hours from the onset of symptoms. It is only the Japanese guideline which has approved of the use of the lower dose (0.6 mg/kg). Also, only a few guidelines explicitly emphasize recommendations on the management of bleeding and angioedema after treatment. Neurosurgical recommendations for the management of malignant infarcts and obstructive hydrocephalous are also clearly defined in medium and high-income countries.

Majority of the clinical trials which looked at the safety and efficacy of the low-dose alteplase were employed among Asians, specifically Japanese. The favorable results of the J-ACT, ENCHANTED, and THAWS trial support the Japanese recommendations [36, 62–64]). Aside from practical reasons of the lower cost from the reduced dose of alteplase (which usually just consumes 1 vial per dose), physiologic advantages such as lower levels of fibrinogen and plasminogen activator inhibitor-1(PAI-1) along with less marked genetic polymorphisms that induces a higher state of coagulation compared to Caucasians have also cited by Ueshima and colleagues [65]. On the other hand, thrombolysis of patients with unclear onset of symptoms but with eligibility according the neuroimaging parameters of the WAKE-UP trial has also made the Australian and the AHA stroke guidelines recommend in favor of the later [66].

It is also interesting to note that of the guidelines reviewed, only three had explicitly stated recommendations on the management of thrombolysis-related complications such as bleeding and angioedema. More so, of the Asian countries included, only Japan had clear statements with this regard. It is equally important to address these limitations especially in resource-limited regions such as Asia and South America, where there is also a scarcity of stroke intensive care units [67, 68].

Encouraging results of various clinical trials for the management of malignant supra and infratentorial infarctions have been instrumental for the increase in confidence for guidelines to recommend these procedures especially for highly eligible patients. While this is of no question for countries with sufficient infrastructure and manpower, it has always been challenging for low- and middle-income countries. In sub-Saharan Africa, it has been previously identified that the ratio of neurosurgeon to population is as low as 1 : 64,000,000 [69]. Furthermore, a study in 2015 on the economic losses attributed to neurosurgical diseases revealed that stroke was a major contributor to the three trillion macroeconomic deficits particularly in low-income countries [70]. It is therefore critical that guidelines be crafted according to individually available resources to ensure optimal implementability.

3.8. Poststroke Rehabilitation. Stroke rehabilitation is another key component of stroke clinical guidelines. Majority put significant weight on early rehabilitation while moderate to weak strengths have been tagged for professional dysphagia assessment. The American, Australian, and UK guidelines likewise put high premium on functional assessment while heterogeneity exists on integrating rehabilitation on comprehensive stroke care center as well as the use of intermittent pneumatic compression for deep vein thrombosis. Majority of the guidelines have weak or no recommendations for depression screening and treatment, as well as regular skin assessment.

One of the aspects of stroke care that most clinicians fail to put attention into is postacute rehabilitation. It is important for healthcare systems to adhere to postsstroke rehabilitation guidelines as various studies have shown that compliance is positively correlated with good clinical outcomes [71–73]. It has also been shown that low-cost rehabilitation with focus on exercise-based and brain training interventions, in resource-deprived settings, still translated to good clinical outcomes [74]. Commensurate rehabilitation initiated within the first seven days of stroke has been shown to initiate complex neurobiological processes which is instrumental in early neurologic recovery as evidenced in various clinical trials [75, 76]. Various clinical settings have also confirmed that poststroke dysphagia results in aspiration pneumonia which further complicates hospital outcomes [77, 78]. Additionally, evidence-based practices for the prevention of deep vein thrombosis such as the use of IPC should likewise be integrated as it may likewise impact on survival [79]. Likewise, there should be increased vigilance for poststroke depression among clinicians as it may occur in more than one third of stroke cases [80]. The need to integrate this in clinical guidelines could not be overemphasized especially in low-income to middle-income countries due to its increasing prevalence [81, 82]. Moreover, its impact on the disability-adjusted life-years lost is significantly greater in than in high-income countries [82].

3.9. Ignored Aspects of Stroke Care. The abundance of sophisticated techniques for stroke care has led clinicians to forget about the basic yet practical aspects of stroke management. It is noted that none of the stroke guidelines incorporate the use of basic immune biomarkers such as the neutrophil to lymphocyte ratio. In the advent of precision medicine nowadays, clinical practice is shifting towards accurate and specific disease characterization, as well as quantifying disease progression and response to therapy, for which biomarkers play critically important role [83]. The neutrophil to lymphocyte ratio is a cheap, readily available, and easy to interpret immune marker which may provide a diagnostic clue particularly for clinical outcomes poststroke [84–86].

Wijeratne and Wijeratne demonstrated the clinical utility of an easily available, universal biomarker (SSIIi) predicting the Post-Covid-19 Neurological Syndrome [87]. It is worth exploring the clinical utility of such biomarkers in the context of poststroke recovery trajectory given the shared pathobiology of these two disorders [88].

While not mentioned in any of the clinical guidelines, the importance of ocular examination in stroke care should not be discounted. Fundus photography is an emerging tool which may assist in differentiating of stroke and TIA from other causes of neurologic deficits, particularly in the emergency setting [89]. Retinal imaging otherwise known as the "window to the brain" may supplement neuroimaging particularly in providing insights for cerebrovascular neurodegenerative conditions [90]. Lastly, it may also provide additional information for identifying stroke etiology, especially that of complicated ones [91]. We have shawn the added value ot low-cost bed side functional vision testing at the bedside in the real world that should be considered in the national and international stroke guidlines [92, 93].

4. Discussion

Stroke and poststroke complications culminate in massive health and economic impacts globally. Stroke occurs in a compromised vascular system. The risk factors associated with stroke (both nonmodifiable risk factors such as genetic, age, and gender and modifiable risk factors such as hypertension, diabetes, high cholesterol, sedentary lifestyle, reduced fruits and vegetable intake, obesity, atrial fibrillation, poor air quality, and smoking) are linked with the build-up of low-grade chronic inflammation that perturbs the homeostasis of the vascular bed prior to the index vascular event such as acute stroke. The newly adopted WHO Intersectoral Global Action Plan calls for immediate action by national international gudiline committees in this regard (https://wfneurology.org/world-brain-day-2022) [94].

The index vascular event leads to a cascade of events that involve bioenergetic failure, disrupted cellular homeostasis, excitotoxicity, acidosis, damaged blood-brain barrier, and cell death very much akin to COVID-19 and brain involvement (Wijeratne and Crewther; https://http://www1.racgp.org.au/ajgp/coronavirus/covid-19-and-long-term-neurological-problems).

Contrary to the traditional belief that the brain and immune systems are physically separate systems, the neural and immune systems are intimately linked through sympathetic nervous system (SNS), hypothalamic pituitary adrenal (HPA) axis, and also through glymphatic systems where bidirectional communication does occur regularly [14, 27, 95, 96].

There were 80.2 million (74.1 to 86.3) prevalent strokes globally in 2016 [41, 97]. Poststroke cognitive impairment has been reported over 50% (which is still a gross underestimation) of stroke survivors with worsened disability and quality of life [42, 98]. Frequency of anxiety after stroke is very high at 24.2% (21.5%-26.9%) by rating scales [43, 99] with likely increased risk of further stroke and downward spiral from the psycho-neuroimmunological PNI point of view. Poststroke depression (PSD) is reported at 18%-33% [44, 100](gross under estimation again, see the comprehensive review on pathobiology of PSD Wijeratne and Sales [19]). Poststroke fatigue (PSF) is reported as one of the worst symptoms by 40% of the stroke survivors with prevalence of PSF that varies from 25% to 85% [45, 46, 101, 102]. Poststroke apathy (PSA) with a prevalence of 34.6% and central poststroke pain (CPSP) with a prevalence that varies from 8% to 55%,can be added to long list of poststroke neurological complications with a similar psycho-neuroimmunological pathobiology to the PCNS as we elaborated in the experimental chapters.

We suggest the desperate need of systems biology approach to all these complications and conder the complete picture with a view to optimize the best immune response after the index event of acute stroke and revisit the current guidelines as a matter of high priority. Such an approach will help the world to address one of the most disabling brain disorders affecting well over 80 million people with excellent value for money with current management approach and also the potential for individualized therapeutic and management avenues (please note that the first submission of this manuscript was published in a preprint server) [103, 104].

5. Conclusion

Stroke management is a dynamic process which has evolved at a very fast pace over the past two decades. With the abundance of clinical trials in this field, it is possible that trends of management now may not be applicable in the future. It is disappointing to see the lack of incorporation of easily accessible, low-cost prognostic markers such as NLR or functional vision assessment at the bed side in any of the published stroke guidelines anywhere in the world. This is despite the fact that large number of publications and metanalyses support the role of NLR in acute stroke as well as in the context of poststroke trajectory. It is therefore imperative for country-specific standard operating procedures to be updated constantly to fit to emerging needs with a systems biology-based approach. Implementability of clinical guidelines is anchored on evidence-based and well-appraised clinical guidelines which are customized according to available resources and to the beliefs of its end-users.

Data Availability

Data that support the findings of this study are available from the corresponding author, [TW], upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Cost-Effectiveness Analysis of Biopharmaceuticals for Treating Rheumatoid Arthritis: Infliximab, Adalimumab, and Etanercept

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Introduction. Rheumatoid arthritis (RA) is a chronic progressive inflammatory disease that causes joint destruction. The condition imposes a significant economic burden on patients and societies. The present study is aimed at evaluating the cost-effectiveness of Infliximab, Adalimumab, and Etanercept in treating rheumatoid arthritis in Iran. *Methods*. This is a cost-effectiveness study of economic evaluation in which the Markov model was used. The study was carried out on 154 patients with rheumatoid arthritis in Fars province taking Infliximab, Adalimumab, and Etanercept. The patients were selected through sampling. In this study, the cost data were collected from a community perspective, and the outcomes were the mean reductions in DAS-28 and QALY. The cost data collection form and the EQ-5D questionnaire were also used to collect the required data. The results were presented in the form of an incremental cost-effectiveness ratio, and the sensitivity analysis was used to measure the robustness of the study results. The TreeAge Pro and Excel softwares were used to analyze the collected data. *Results*. The results showed that the mean costs and the QALY rates in the Infliximab, Adalimumab, and Etanercept arms were $ 79,518.33 and 12.34, $ 91,695.59 and 13.25, and $ 87,440.92 and 11.79, respectively. The one-way sensitivity analysis confirmed the robustness of the results. In addition, the results of the probabilistic sensitivity analysis (PSA) indicated that on the cost-effectiveness acceptability curve, Infliximab was in the acceptance area and below the threshold in 77% of simulations. The scatter plot was in the mentioned area in 81% and 91% of simulations compared with Adalimumab and Etanercept, respectively, implying lower costs and higher effectiveness than the other two alternatives. Therefore, the strategy was more cost-effective. *Conclusion*. According to the results of this study, Infliximab was more cost-effective than the other two medications. Therefore, it is recommended that physicians use this medication as the priority in treating rheumatoid arthritis. It is also suggested that health policymakers consider the present study results in preparing treatment guidelines for RA.

1. Introduction

Rheumatoid arthritis (RA) is a progressive inflammatory disease characterized by inflammation of the synovial membrane and may eventually lead to joint destruction [1, 2]. Due to its long-term chronic and safety course, it is immediately required to treat with immunomodulatory medications [3]. This debilitating condition is supposed to affect 0.3-1.2%

of the world's population [4]. Uncontrolled RA leads to progressive joint destruction and performance reduction [5]. These conditions impose a significant underlying economic burden, reduce the quality of life (QOL), and lead to productivity loss [6]. Disease-modifying antirheumatic medications (DMARDs) such as Methotrexate, Sulfasalazine, and Hydroxychloroquine may delay the disease progression [7]. However, many patients do not achieve an appropriate response, and some do not maintain a reaction due to ineffectiveness or toxicity [8].

Nowadays, physicians are trying to achieve less disease activity or, preferably, recovery, rather than simply slowing the progression of the disease and controlling the symptoms [9]. Biopharmaceuticals are drugs that are obtained from biological sources by biotechnological methods [10–12]. The more important these drugs become in medicine, the more attention is paid to concerns such as biosimilars, cost-effectiveness, and price control. The therapeutic value of biopharmaceuticals for the healthcare system is not yet well understood, and this only happens when policymakers understand the effects of these biological products on the economic system of healthcare facilities [13, 14]. The discovery of biopharmaceuticals leads to a dramatic change in the therapeutic approach to RA and results in better QOL [15]. However, success requires the purchase of these medications at high prices [4, 5], which may ultimately increase the financial burden that RA imposes on the community. Such a scenario represents the need for pharmacoeconomics evaluations to inform policymakers and decision-makers about the cost-effectiveness of biological DMARDs [5, 16].

TNF inhibitors are a class of biopharmaceuticals applicable for treating Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and/or juvenile idiopathic arthritis. According to the FDA, this category of medicines includes Infliximab, Etanercept, Adalimumab, Certolizumab pegol, and Golimumab. Although the side effects of these medicines are not yet fully understood, several side effects are still under investigation. Some of these well-known adverse effects are bacterial, fungal, viral, or atypical infections, the risk of malignancies, especially lymphomas, congestive heart failure NYHA Class III or IV, drug-induced lupus demyelinating disorders, including optic neuritis, multiple sclerosis, and local injection site reaction/erythema. Infliximab is a chimeric monoclonal antibody composed of fixed human and variable mouse regions [17]. This medication can only be used intravenously and should be used in combination with Methotrexate if possible. The starting dose of the medicine is 3 mg per kg of body weight and can be increased up to 10 mg/kg with an interval of 4-8 weeks. In mid-2001, the FDA/EMA approved Infliximab combined with Methotrexate to treat RA [18].

Infliximab inhibits TNF-α binding to its target receptors and prevents the production of other proinflammatory cytokines, including interleukin and GCSF [19]. Common side effects of infliximab therapy include acute injection reactions, infections, and delayed hypersensitivity reactions. The medication is contraindicated in people with moderate to severe heart failure and tuberculosis or other severe or opportunistic infections [20]. Adalimumab is a recombinant human IgG1 monoclonal antibody with no mouse ingredient produced by phage display technology. The FDA/EMA approved it in 2002 to treat moderate to severe RA to be used alone or in combination with other DMARDs. Adalimumab is injected subcutaneously every two weeks [21]. The common side effects of the medication include injection reactions and site infection. Adalimumab is contraindicated in people with moderate to severe heart failure and active TB or people with other severe or opportunistic infections. Before starting the treatment, physicians should examine the patients for active and inactive (latent) tuberculosis infection [20]. Etanercept is also a recombinant human TNF receptor fusion protein that attenuates the effects of endogenous TNF by competitively inhibiting its interaction with cell surface receptors. Etanercept has been proved to be effective in patients with rheumatoid arthritis and is injected subcutaneously at 25 or 50 mg once or twice a week [22].

Considering different medical costs, medication of various financial and economic consequences of these biopharmaceuticals is not clear on the health system, and there is limited knowledge about their cost-effectiveness. Since the researchers could not find any studies that have compared these medications' cost-effectiveness, the present study was conducted to determine and compare the cost-effectiveness of Infliximab, Adalimumab, and Etanercept for patients with RA.

2. Materials and Methods

This is a cross-sectional study for the economic evaluation of cost-effectiveness in patients with RA in Fars province in 2019. The study population included all the patients with RA referred to the rheumatology department of Hafez Hospital and the rheumatologists' offices in 2019 and who were treated with one of the following three medications: Adalimumab, Infliximab, and Etanercept. The sample sizes of the patients treated with Adalimumab, Infliximab, and Etanercept based on previous studies, 80% power, and 5% error using the NCSS statistical software were 48, 53, and 53, respectively.

2.1. Description of the Model. In this study, the Markov model was used to evaluate the cost-effectiveness of Infliximab, Adalimumab, and Etanercept for treating patients with RA and describing the progression of the disease. As in previous studies, three-month Markov cycles and the time horizon until the end of life were considered.

The Disease Activity Score-28 (DAS-28 due to the evaluation of 28 joints) was used to show the clinical course of the disease. DAS-28 is a standard measure of RA activity, and the score it provides indicates whether the current treatment has worked for the patient. The doctor or nurse calculates the DAS-28 with a special calculator based on several tests, including joint examinations, blood tests, and a self-assessment of how the condition is felt during the investigations. As a rule, the lower the DAS-28 score, the better the patient's condition has been controlled. More severe joint damage is often associated with a higher DAS-28 score [23, 24]. Figure 1 shows a schematic diagram of the Markov model for RA.

The costs and outcomes used in the model were discounted based on the discount rates of 5.8% [25] and 3% [26], respectively. Furthermore, Microsoft Excel and TreeAge Pro softwares were used to analyze the collected data.

2.2. Transition Probabilities. All transition probabilities are reported in Table 1, based on the previously published studies.

2.3. Cost Data. In this study, the societal perspective was used to extract the costs. The related costs from a societal perspective included direct medical costs (DMC), direct nonmedical costs (DNMC), and indirect costs (IC). DMC related to each of the three medications were retrospectively collected from January 1, 2019, to December 31, 2019, using a researcher-made checklist by referring to the rheumatology department of Hafez Hospital and the personal offices of rheumatologists. DNMC, as well as IC, were also collected using the cost data collection form and the patients' self-report. The human capital approach was applied to calculate the indirect costs.

Furthermore, for international comparisons, the costs were converted into dollars (PPP) using international dollars using a purchasing power parity (PPP) $ exchange rate of 22075 rials per 1 $ rial in 2019 [29].

2.4. Utility Data. Utility values were also extracted using the EQ-5D questionnaire, and the health outcomes were evaluated based on quality-adjusted life years (QALY) [30]. To measure the utility scores, we carried out face-to-face interviews or telephone calls with 154 RA patients in 2019.

The interviews were conducted with the outpatients referring to the hospitals and clinics affiliated to Shiraz University of Medical Sciences. It should be noted that an EQ-5D questionnaire is a standard tool for measuring health outcomes, introduced by the EuroQol Group in 1990 (https://euroqol.org/). It includes five questions on five aspects of mobility, self-care, routine activities, pain/discomfort, and anxiety/depression. The respondents' scores range from 0 to 1, and higher scores mean better utility. The patients with RA who were willing to participate in this study were interviewed accordingly. Once the EQ-5D questionnaire was completed, the values of Iran, determined in a separate survey of Goudarzi et al. [31] using time trade-off (TTO), were considered, and the 5-digit codes of the questionnaire were changed to numerical utility.

2.5. Incremental Cost-Effectiveness Ratio (ICER). After obtaining the costs and utilities through the previous steps, the incremental cost-effectiveness ratio (ICER) was calculated using the following formula:

$$\text{ICER} = \frac{\text{Cost}A - \text{Cost}B}{\text{Outcome}A - \text{Outcome}B}. \quad (1)$$

2.6. Uncertainty Analysis. Finally, the one-way sensitivity analysis and probabilistic sensitivity analysis (PSA) were used to investigate the effects of parameter uncertainty on the results. To do the one-way sensitivity analysis, some critical parameters of the study, such as cost and utility, were changed by 20% for each medication strategy. Then, the results were presented in the form of a Tornado diagram. Also, the PSAs were conducted since the utility and cost variables in the present study were measurable and probabilistic, and they were considered distributions so that beta distribution (β) was used to determine the distribution of utility values (0 to 1). The gamma distribution was also used to determine the cost distribution, based on which second-order Monte Carlo simulation was performed using 5000 trials. The PSA results are presented using the cost-effectiveness acceptability curve and the incremental cost-effectiveness scattered plot. The cost-effectiveness acceptability curve is one of the best curves for planning and policy-making. It can help the policymakers and planners of the health system measure the cost-effectiveness probability of each intervention in return for willingness to pay for the expenses. On the other hand, the scatter plot provides more detailed information in individual comparisons. It indicates the percentage of the points in the acceptance area, i.e., below the threshold [32].

An explicit threshold for willingness to pay (WTP) is not available in Iran. Therefore, according to WHO suggestion for developing countries, the willingness to pay was determined as one to three times the gross domestic product (GDP) per capita QALY [33]. GDP was about $ 12547 in Iran in 2019, used as the threshold for willingness to pay [34].

3. Results

According to the present study results, a majority of the patients were females (73.37%) and housewives (62.33%), and all the patients had insurance coverage. Besides, 94.34%, 87.5%, and 88.68% of those treated with Infliximab, Adalimumab, and Etanercept were 18-65 years old, respectively. Given that in economic studies, the ages 18 to 65 are considered the productivity ages, they are economically significant.

Table 2 shows the mean costs of RA patients using Infliximab, Adalimumab, and Etanercept. According to this table, the mean direct medical expenses of the patients taking Infliximab, Adalimumab, and Etanercept were $ 9004, $ 10046, and $ 10677, respectively, while the direct nonmedical costs were $ 2484.67, $ 2099.47, and $ 556.76, respectively. Furthermore, the costs of purchasing the primary medication were the highest direct medical costs of the patients using all three medicines (Infliximab: $ 7110.39, Adalimumab: $ 8582.42, and Etanercept: $ 9171.32). The indirect costs were also $ 186.53, $ 192.62, and $ 172.82 (PPP) for the patients taking Infliximab, Adalimumab, and Etanercept.

In general, according to Table 2, the total treatment costs for Infliximab, Adalimumab, and Etanercept were $ 11,675.21, $ 12337.62, and $ 11406.79, respectively. Thus, the cost of treatment with Etanercept was the lowest.

As shown in Table 2, the number of people whose DAS-28 (biologic medication threshold) dropped from 5.1 to <2.6 was 27 (51%), 33 (68.75%), and 29 (54.72%) in the case of Infliximab, Adalimumab, and Etanercept, respectively.

According to QALY, the highest utility scores of the patients with RA obtained from the EQ5D questionnaire were those of the patients using Etanercept who had DAS-28 < 2.6 (0.891).

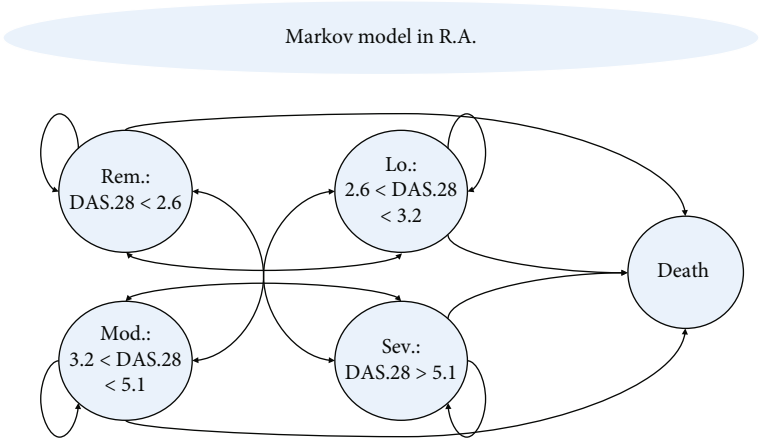

Figure 1: Schematic design of the Markov model for rheumatoid arthritis. Rem: remission; Lo: low; Mod: moderate; Sev: severe.

Table 1: Transition probabilities used in the Markov decision model.

Stage	Remission	Low	Moderate	Severe	Death
Remission	0.500	0.310	0.119	0.070	0.001
Low	0.262	0.388	0.306	0.040	0.004
Moderate	0.070	0.217	0.550	0.155	0.008
Severe	0.020	0.040	0.307	0.621	0.012
Source		[27]			[28]

As shown in Figure 2 and Table 3, the results of utility cost analysis using the Markov model showed that the mean costs and QALY in Infliximab, Adalimumab, and Etanercept arms were $ 79,518.33 and 12.34, $ 91,695.59 and 13.25, and $ 87,440.92 and 11.79, respectively. These results indicate that treatment with Infliximab or Adalimumab was predominant over treatment with Etanercept and was more cost-effective. However, the cost-effectiveness ratio calculated for Adalimumab treatment compared to Infliximab was $ 13,420.09, suggesting that $ 13,420.09 had to be spent for each additional QALY in the patients treated with Adalimumab. In this case, ICER had to be compared with the threshold to decide. The method provided by the WHO was used to calculate the threshold; thus, if the ICER were lower than one times GDP per capita, the program would be much cost-effective, and if it were lower than three times GDP per capita, the program would be cost-effective [33]. The GDP per capita was $ 12547 in 2019 [34]. Besides, considering that the ICER was $ 13,420.09, more than one times GDP per capita, Adalimumab treatment was not more cost-effective than Infliximab treatment due to the ICER of over one times threshold.

3.1. Uncertainty Analysis

3.1.1. One-Way Sensitivity Analysis. Figure 3 shows the percentage of change in the incremental cost-effectiveness ratio in treating Infliximab vs. Adalimumab. The total cost-effectiveness ratio is also presented with $ 13,420.12. According to the Tornado diagram results, ICER had the highest sensitivity to the reduction of utility in the treatment with Adalimumab in remission mode and the minor sensitivity to the decrease in other costs of Adalimumab in the weak state of the disease. Therefore, if utility in the treatment with Adalimumab changes in remission mode, considering that the ICER value will still become a positive number, it cannot be decided with certainty that Infliximab has superiority over Adalimumab.

Figure 4 shows the percentage of change in the incremental cost-effectiveness ratio of Infliximab treatment compared to the treatment with Etanercept. The number $ -14,348.30 indicates the incremental cost-effectiveness ratio. The Tornado diagram results show that ICER was the most sensitive to reducing utility in treatment with Infliximab in an intermediate state and had the least sensitivity to the reduction of other utilities of the Infliximab in the low and remission states. Furthermore, given that in this case, the ICER value was again negative, it could be decided with certainty that Infliximab was superior to Etanercept.

3.2. Probabilistic Sensitivity Analysis (PSA). The PSA results were uncertainly presented using the cost-effectiveness acceptability curve and the incremental cost-effectiveness scattered plot. The acceptability curve result based on QALY shows that Infliximab was below the cost-effectiveness threshold of $ 12547 PPP (one times GDP) in 77% of the simulations and, therefore, was the most cost-effective medication therapy strategy (Figure 5).

In addition, the results of the scatter plots based on QALY (Figures 6(a) and 6(b)) showed that compared to Adalimumab and Etanercept, Infliximab was in the acceptance area and below the threshold in 81% and 91% of the

Table 2: Mean costs and utility of rheumatoid arthritis patients using Infliximab, Adalimumab, and Etanercept (in terms of purchasing power parity).

Costs	Infliximab		Adalimumab		Etanercept	
	PPP	%	PPP	%	PPP	%
Direct medical cost						
Visits	172.14	1.91	172.14	1.71	172.14	1.61
Medication	7110.39	78.97	8582.42	85.44	9171.32	85.90
Tests	618.40	6.87	618.40	6.16	618.40	5.79
Physiotherapy and other expenses	410.41	4.56	387.60	3.86	439.37	4.03
Diagnostic services	284.96	3.16	284.96	2.84	284.96	2.67
Injection cost	407.70	4.53	0.00	0.00	0.00	0.00
Total	9004.00	77.12	10045.53	81.42	10677.20	93.60
Direct nonmedical cost						
Transportation	1451.79	58.43	1285.51	61.23	318.02	57.12
Accommodation	580.92	23.38	435.22	20.73	125.22	22.49
Meals	451.96	18.19	378.74	18.04	113.52	20.39
Total	2484.67	21.28	2099.47	17.02	556.76	4.88
Indirect cost						
Lost revenue	186.53	1.60	192.62	1.56	172.82	1.52
Total cost	11675.21	100	12337.62	100	11406.79	100
Effectiveness	Number	%	Number	%	Number	%
DAS-28 < 2.6	27	50.94	33	68.75	29	54.72
2.6 < DAS-28 < 3.2	17	32.07	2	4.2	5	9.43
DAS-28 > 3.2	9	16.98	13	27.08	19	38.85
Utilities	Mean	Sd	Mean	Sd	Mean	Sd
DAS-28 < 2.6	0.836	0.196	0.725	0.193	0.891	0.126
2.6 < DAS-28 < 3.2	0.717	0.148	0.656	0.223	0.337	0.276
3.2 < DAS-28 < 5.1	0.23	0.216	0.437	0.209	0.391	0.211
DAS-28 > 5.1	0.2	0.170	0.23	0.190	0.223	0.190

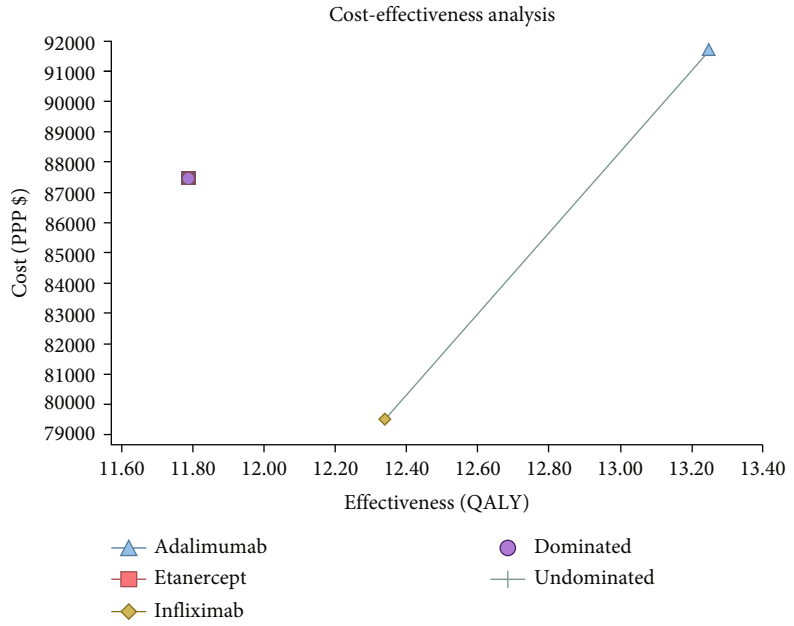

Figure 2: Cost-effectiveness plan for treatment with Infliximab, Adalimumab, and Etanercept in patients with RA.

Table 3: Results of cost-utility analysis for rheumatoid arthritis patients treated with Infliximab, Adalimumab, and Etanercept.

Strategy name	Cost (PPP$)	QALYs	Incremental cost	Incremental utility	ICER (incremental cost per QALY gained) PPP$
Infliximab	79,518.33	12.34	0.00	0.00	0.00
Etanercept	87,440.92	11.79	7,922.59	-0.55214	Abs. Dominated
Adalimumab	91,695.59	13.25	12,177.26	0.90739	13420.09

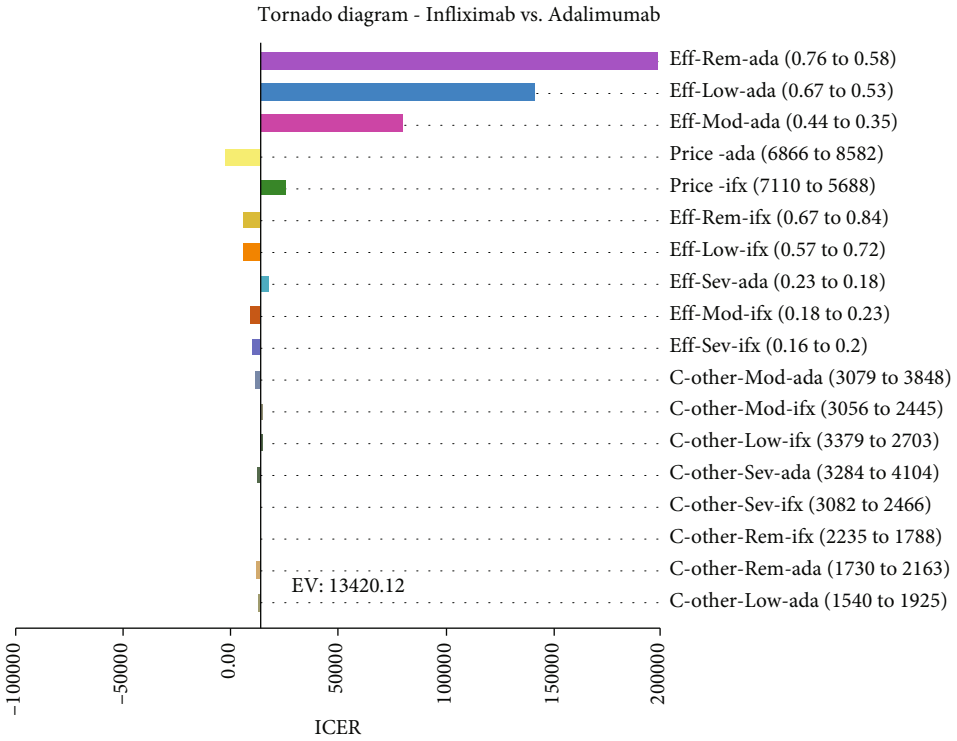

Figure 3: Tornado diagram for one-way sensitivity analysis of Infliximab and Adalimumab treatments. ifx: Infliximab; ada: Adalimumab; rem: Remission; mod: moderate; sev: severe; eff: effectiveness; c: cost.

simulations, respectively. This result indicates lower cost- and higher effectiveness than the other two alternatives and, therefore, is a more cost-effective strategy.

4. Discussion

For the first time, this study was conducted to evaluate the cost-effectiveness of Infliximab, Adalimumab, and Etanercept in patients with RA in Iran. This study is aimed at comparing three medicines that act against TNF-alpha, which was widely used to treat RA. All three medicines are considered equally effective in terms of clinical value for physicians, and the main difference is in their price. Therefore, the subject of the present study was which ones are more cost-effective used against TNF-alpha? All three medicines studied in this research are used subcutaneously through an autoinjector pen and are no different in this regard.

According to the present study findings, treatment with Infliximab, Adalimumab, and Etanercept had a mean cost of $ 11,675.21, $ 12,337.62, and $ 11,406.79 PPP, respectively, for each one-year treatment course. Thus, the mean treatment cost per patient taking Etanercept was lower than treatment with the two other medications. In this regard, the results are consistent with those of the studies by Tang et al., Carter et al., and Ramírez-Herráiz et al. [35–37].

The DMC, DNMC, and IC of the patients using Infliximab were $ 9004.00 (77.12% of the total costs), $ 2484.67 (21.28% of the total costs), and $ 186.53 (1.60% of the total costs) PPP, respectively. However, the prices of patients paid for Adalimumab were $ 10045.53 (81.42% of the total costs), $ 2099.47 (17.02% of the total costs), and $ 192.62 (1.56% of the total costs) PPP, respectively, and those of the patients paid for taking Etanercept were $ 10677.20 (93.60% of the total costs), $ 556.76 (4.88% of the total costs), and $ 172.82 (1.52% of the total costs) PPP. Meanwhile, the cost of purchasing the primary medication was the highest direct medical cost of the patients using all the three medications (Infliximab: $ 7110.39 PPP (78.97% of the total costs); Adalimumab: $ 8582.42 PPP (85.44% of the total costs); and Etanercept: $ 9171.32 PPP (85.90% of the total costs)). The results of this study are consistent with those of Incerti et al., Soini et al., Bonafede et al., Lekander et al., and Saraux et al. [38–42].

The results of this study showed that the number of the patients whose DAS-28 dropped from 5.1 (biologic medication

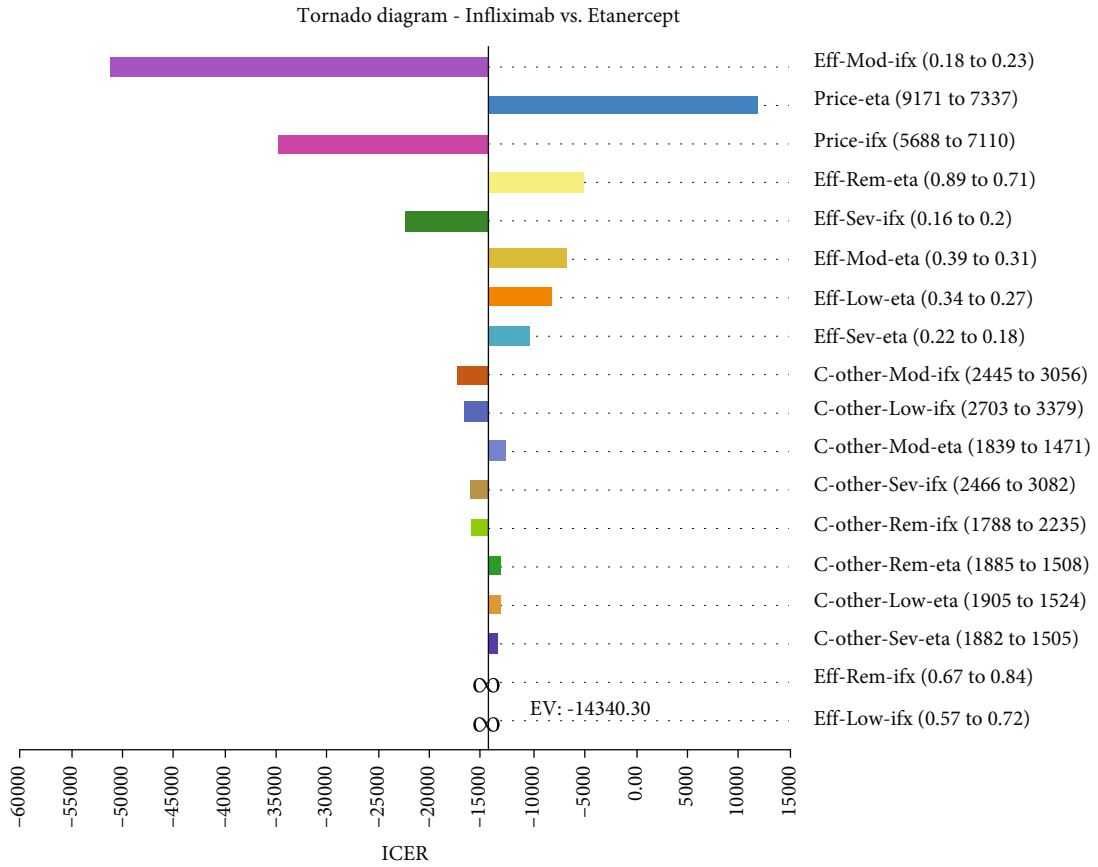

Figure 4: Tornado diagram of one-way sensitivity analysis for Infliximab and Etanercept treatments. ifx: Infliximab; eta: Etanercept; rem: Remission; mod: moderate; sev: severe; eff: effectiveness; c: cost.

threshold) to <2.6 in the Infliximab, Adalimumab, and Etanercept groups was 27 (51%), 33 (68.75%), and 29 (54.72%), respectively. This result indicates that Adalimumab was the most effective medication.

A study carried out by Cárdenas et al. examined the cost-effectiveness of Infliximab, Adalimumab, and Etanercept over two years showing that Adalimumab was more effective than the other two medications [43]. Furthermore, the results of the study by Wiens et al. that entitled the analysis of effectiveness and safety of Adalimumab, Etanercept, and Infliximab for the treatment of RA indicated that short-term therapy with Etanercept and Adalimumab was most effective, while long-term treatment with Adalimumab was the most effective [44].

In a study entitled direct comparison of therapeutic responses, disease control, and medication adherence in patients with RA treated with Adalimumab, Etanercept, and Infliximab, Hetland et al. (2009) concluded that Infliximab had the lowest therapeutic response, the lowest rate of recovery, and the lowest rate of medication adherence. However, Adalimumab had the highest therapeutic response and remission rate, while Etanercept had the highest medication adherence [45]. In this respect, the results are consistent with the findings of the present study.

The study results by Santos-Moreno et al. conducted as a cohort in Colombia to directly compare the effectiveness of Adalimumab, Etanercept, and Infliximab showed that in the beginning, the DAS-28 was 4.1 but it changed to 2.39 after 36 months. The most common complication was dermatitis. It was finally concluded that all three medications reduced the severity of the disease, and Etanercept had a lower incidence of side effects than the other two medications. It is in line with the present study regarding the effectiveness of all three medications in reducing the symptoms and controlling the disease [46].

According to the present study results, the highest utility of each medication was found in the patients with DAS-28 < 2.6, and as the Disease Activity Score-28 (DAS-28) increased, the life desirability decreased. As the Disease Activity Score-28 (DAS-28) increased, more joints got involved in the disease, and the effect of the medications was usually reduced. Therefore, the patients entered the severe phase of the disease, and it could be natural that their life desirability decreased [47].

The cost-utility analysis results using the Markov model showed that the mean costs and QALY amount in the Infliximab, Adalimumab, and Etanercept arms were $ 79,518.33 and 12.34, $ 91,695.59 and 13.25, and $ 87,440.92 and 11.79, respectively. Thus, treatment with Infliximab or Adalimumab was predominant over Etanercept and was also more effective. Besides, the comparison of the threshold introduced by the WHO (one times GDP-per capita) and

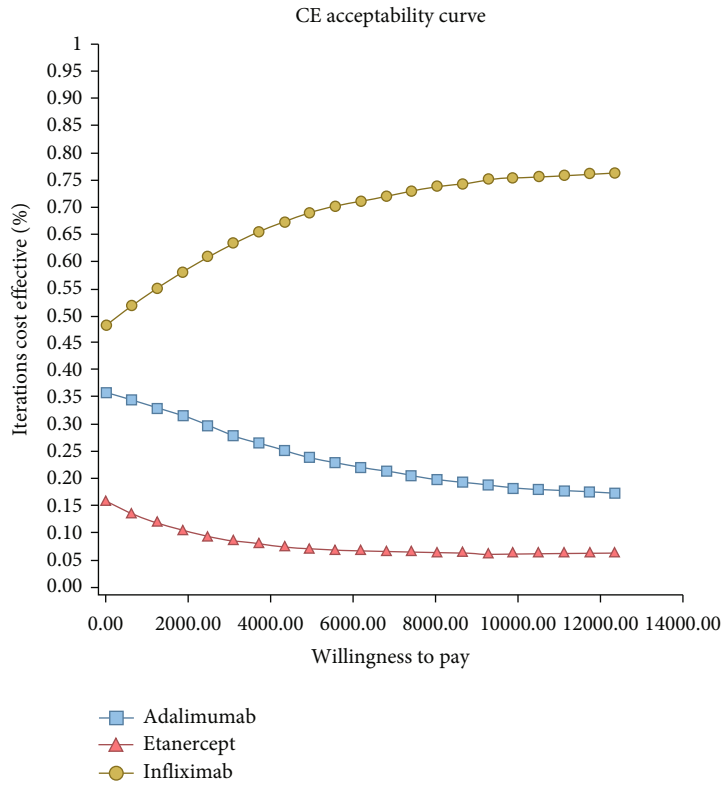

Figure 5: Cost-effectiveness acceptability curve of Infliximab, Adalimumab, and Etanercept obtained through Monte Carlo simulation.

the incremental cost-effectiveness ratio (ICER) was obtained by comparing Adalimumab and Infliximab indicated that Infliximab was a more cost-effective option.

In their study entitled cost analysis and application of second-line treatment with Rituximab in comparison with Tumor Necrosis Factor Inhibitors in RA, Lopatina et al. showed that over a one-year time horizon, Rituximab and Etanercept resulted in the effectiveness of 0.80 QALYs with the costs of $ 14,291 and $ 18,880, respectively. They were the dominant choices compared to Adalimumab ($ 0.79 QALYs, $ 18,825) and Infliximab (0.76 QALYs, $ 20158). Also, over a 6-year time horizon, Rituximab (4.42 QALYs ($ 82,402) was predominant compared to Adalimumab (4.30 QALYs, $ 101,420), Etanercept (4.02 QALYs, $ 99,191), and Infliximab (3.71 QALYs, $ 100,396). In a probabilistic analysis, Rituximab was predominant over Adalimumab, Etanercept, and Infliximab with the probabilities of 0.51, 0.62, and 0.65, respectively [48].

Zrubka et al. conducted a systematic study and evaluated the long-term efficacy and cost-effectiveness of Infliximab as a first-line treatment for RA. The results showed that the recovery of the RA patients treated with Infliximab was significant within six months compared to the control group. Over a year, the improvement was remarkable in those who used Infliximab than the control strategies [47]. In this respect, the results are consistent with those of the present study.

In Taiwan, Chen et al. examined the cost-effectiveness of Tofacitinib vs. Adalimumab and concluded that the QALY obtained in treatment with Tofacitinib was 0.09 more than Adalimumab (5.13 vs. 5.04). Besides, the incremental cost-effectiveness was 143122 QALY/$ NT. The one-way sensitivity analysis confirmed that the results were robust [49]. These results are in line with those of the present study.

Fatemi et al. conducted a study in Iran and examined the cost-effectiveness of Tofacitinib vs. Adalimumab and Etanercept. They concluded that Tofacitinib was more cost-effective than the two others, and although Tofacitinib had fewer QALYs than Etanercept (6.664 vs. 6.876), it cost less on the lifetime horizon ($ 42,565.04 vs. $ 58,696.29). Tofacitinib also cost less than Adalimumab ($ 50,299.91 vs. $ 51,550.29) and had more QALYs (6,900 vs. 6,687). The sensitivity analysis also showed that the results were sensitive to the cost of the medications [50]. These findings are in line with those of the present study.

In a study in Brazil entitled the cost-effectiveness analysis of RA medications, dos-Santos et al. suggested that Golimumab was the most effective medication. It was also the dominant option compared to Etanercept. On the other hand, the Adalimumab ICUR was $ 95,095.37. The sensitivity analysis indicated that the results were robust [51].

The results of a study by Chastek et al. on the comparative efficacy of TNF blockers in RA patients treated with Adalimumab, Etanercept, and Infliximab from January 1, 2006, to 2008 showed that Etanercept had the lowest dose and the patients showed the best response to Infliximab [52]. This study is in line with the results of the present study.

In their study entitled "biological medications for RA in Medicare: Cost-Effectiveness Analysis", Wailoo et al. concluded that the efficacy of Infliximab, Adalimumab, and Etanercept in the treatment population was similar, but

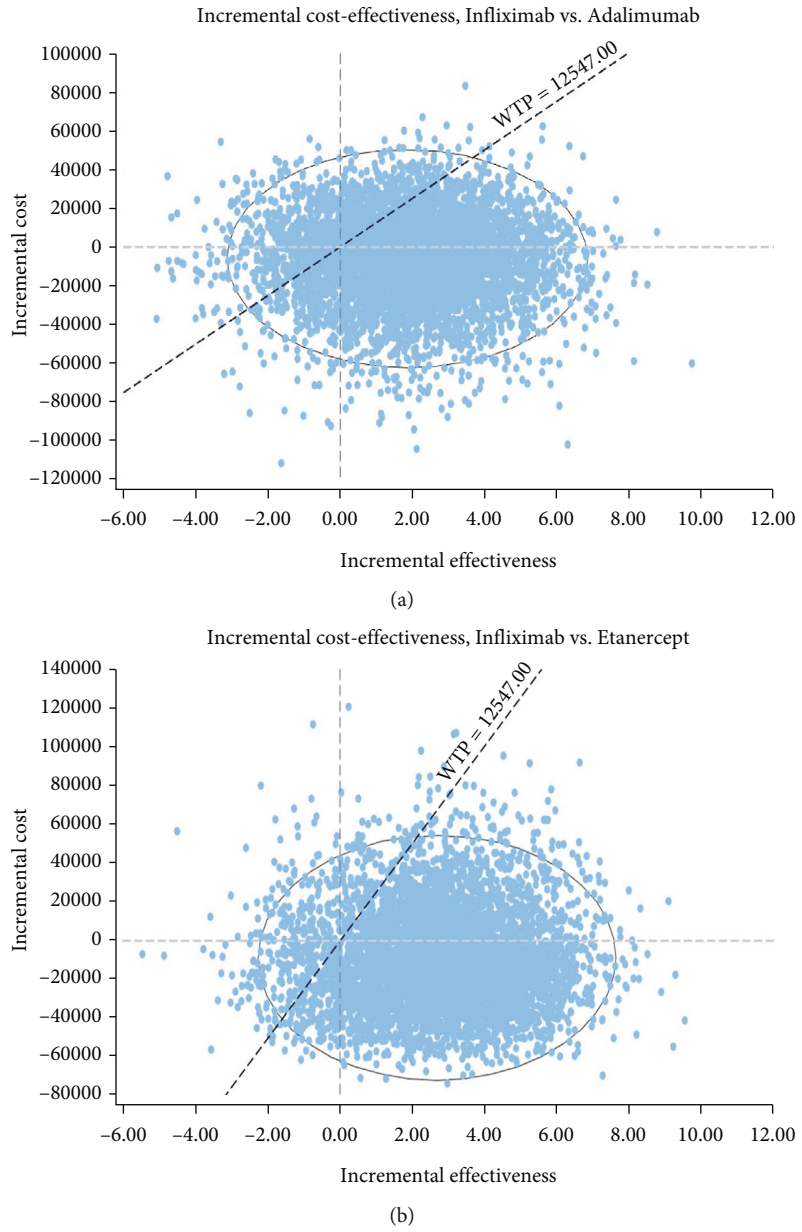

Figure 6: Scatter plot of incremental cost-effectiveness of Infliximab compared with Adalimumab and Etanercept.

Infliximab was more costly [53]. This conclusion might be due to the higher price of this medication.

Curtis et al. conducted a study on the cost-effectiveness of biological medications in RA patients with commercial insurance, in which the subjects were 18 to 63 years old. They finally indicated that Etanercept was the most cost-effective option [54]. Their study results are inconsistent with the present research, which could be the lower price of Etanercept compared to other medications.

Also, the one-way sensitivity analysis results on Infliximab and Etanercept confirmed the robustness of the study results and indicated that Infliximab could be a superior medication compared to Etanercept.

The probabilistic sensitivity analysis results showed that on the cost-effectiveness acceptability curve, Infliximab was in the acceptance area and below the threshold in 77% of the simulations. The medication was also in the acceptance area of cost-effectiveness scattered plot, e.g., below the threshold in 81% and 91% of the simulations compared to Adalimumab and Etanercept. This finding indicates its lower costs and higher effectiveness than the other two alternatives, and therefore, the strategy was more cost-effective.

The present study had some limitations as the limited data required, especially for the disease transition probabilities. Hence, fixed rates were used in this study. In addition, intangible costs were not calculated in this study due to the impossibility of measuring them accurately.

Regarding the generalizability of the results, it can be said that since the medications are used in all provinces and medical centers of Iran to treat RA patients and their

prices are the same throughout the country, the results of this study can be generalized to other provinces and the whole country. However, it is necessary to consider the following items to generalize the results to other countries: epidemiology of the disease and demographic structure, existence of resources, prices, evaluation of outcomes by individuals, threshold, and the use of various effectiveness indicators in different studies that may affect the results of the present study. Therefore, caution is needed when generalizing the results to other countries.

According to the results of this study, Infliximab was more cost-effective than the other two medications. Therefore, based on the sensitivity analysis results, as long as the study parameters do not change significantly, it is suggested that Infliximab should be used as the priority for treating patients with RA. Also, health policymakers and managers should try to increase insurance coverage and reduce out-of-pocket payments.

Data Availability

All data used to support the findings of this study are included within the article.

Ethical Approval

The study protocol was approved by the Ethics Committee of Shiraz University of Medical Sciences under the ethical code IR.SUMS.REC.1399.100. All participants were informed both verbally and through written information of their right to withdraw from the study at any time.

Consent

All participants gave their written consent to participate in the study.

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

AGH participated in the study's design, supervised the whole study, and revised the paper critically for important intellectual content. JA is assigned to the study concept and design and participated in literature bibliography, acquisition of data, analysis, and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. EA drafted the manuscript and revised the paper. MR participated in the analysis of data, drafting of the manuscript, and editing the article. KHK participated in the design of the study, drafting of the manuscript, and final revision. All authors read and approved the final manuscript.

Acknowledgments

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Research Article

Utilisation Trend of Long-Acting Insulin Analogues including Biosimilars across Europe: Findings and Implications

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Background. Diabetes mellitus rates and associated costs continue to rise across Europe enhancing health authority focus on its management. The risk of complications is enhanced by poor glycaemic control, with long-acting insulin analogues developed to reduce hypoglycaemia and improve patient convenience. There are concerns though with their considerably higher costs, but moderated by reductions in complications and associated costs. Biosimilars can help further reduce costs. However, to date, price reductions for biosimilar insulin glargine appear limited. In addition, the originator company has switched promotional efforts to more concentrated patented formulations to reduce the impact of biosimilars. There are also concerns with different devices between the manufacturers. As a result, there is a need to assess current utilisation rates for insulins, especially long-acting insulin analogues and biosimilars, and the rationale for patterns seen, among multiple European countries to provide future direction. *Methodology*. Health authority databases are examined to assess utilisation and expenditure patterns for insulins, including biosimilar insulin glargine. Explanations for patterns seen were provided by senior-level personnel. *Results*. Typically increasing use of long-acting insulin analogues across Europe including both Western and Central and Eastern European countries reflects perceived patient benefits despite higher prices. However, activities by the originator company to switch patients to more concentrated insulin glargine coupled with lowering prices towards biosimilars have limited biosimilar uptake, with biosimilars not currently launched in a minority of European countries. A number of activities were identified to address this. Enhancing the attractiveness of the biosimilar insulin market is essential to encourage other biosimilar manufacturers to enter the market as more long-acting insulin analogues lose their patents to benefit all key stakeholder groups. *Conclusions*. There are concerns with the availability and use of insulin glargine biosimilars among European countries despite lower costs. This can be addressed.

1. Introduction

Global expenditure on medicines is envisaged to reach US$1.5 trillion by 2023 enhanced by growing prevalence rates for noncommunicable diseases (NCDs) [1, 2]. This is a concern among European countries given their desire to retain universal healthcare as a core principle as well as limit out-of-pocket expenditures especially among citizens with low income [3–6]. Currently across Europe, approximately one-fifth of health spending is paid for out of pocket, with a higher proportion among those with low income potentially leading to catastrophic consequences [4].

One NCD of increasing priority is diabetes mellitus, where prevalence rates grew to 463 million people worldwide in 2019 [7, 8]. In Europe, approximately 59 million people are currently estimated to have diabetes, with this number predicted to rise to 68 million by 2045 [9]. Whilst the majority of these patients will have type 2 diabetes (T2DM), up to 30% or more of patients with diabetes require insulin to help control HbA1c levels [10–13].

As a result of growing prevalence rates, the global economic burden of diabetes is envisaged to be as high as 2.2% of Gross Domestic Product (GDP) by 2030 [14], supported by GDP growth rates worldwide across many countries including developing countries [15, 16]. The economic impact of diabetes is enhanced by the cost of the complications including complications arising from hypoglycaemia [9, 13, 17, 18]. This is important with estimated rates of hypoglycaemia up to 3.5–3.6 events/month among patients with type 1 diabetes (T1DM) and 2.2–3.7 among those with type 2 diabetes (T2DM) [19–23], with some authors finding that rates of hypoglycaemia may be similar for T2DM

patients taking insulins for >5years [13]. In addition, the serious consequences of hypoglycaemia may turn out to be greater in T2DM patients, particularly regarding the effects on the cardiovascular system [13]. Overall, diabetes is among the leading causes of nontraumatic lower extremity amputation and blindness worldwide, with patients with diabetes also at greater risk of cardiovascular disease [7, 24–26]. In view of this, it is important that patients with diabetes should be carefully managed, which includes reducing the risk of hypoglycaemia [13].

Long-acting insulin analogues were specifically developed to lower the risk of hypoglycaemia in patients with diabetes requiring insulin, especially nocturnal hypoglycaemia, as well as improve patient convenience through reducing the number of injections thereby enhancing adherence rates, which is a continuing concern with insulin [7, 9, 27–30]. There is still controversy though regarding the level of benefit seen with long-acting insulin analogues versus NPH and other insulins [31–33]. However, a recent systematic review and network meta-analysis suggests that long-acting insulin analogues were superior to intermediate-acting insulins in key areas including major, serious, and nocturnal hypoglycaemia [34]. Having said this, the perceived patient benefits of long-acting insulin analogues are potentially reflected by their usage now typically exceeding that of human insulins in upper-middle and high-income countries as well as growing in lower middle-income countries including Bangladesh [35–37]. In addition, global expenditure on insulin glargine was already US$3.88 billion in 2018 out of a total market of US$24million and envisaged to potentially reach as high as US$9.26 billion by 2025 helped by growing sales of Toujeo® 300 IU/ml [38, 39]. Expenditure on insulin detemir was US$2.7 billion in 2015, growing at 7.5% per year [40], with sales of insulin degludec also growing with studies demonstrating their improved effectiveness and cost-effectiveness versus other long-acting insulin analogues [41–45].

However, there are concerns with the high costs of long-acting insulin analogues compared to Neutral Protamine Hagedorn (NPH) and other insulins [31, 35, 46]. This is not universal though with published studies showing that the higher acquisition costs of long-acting insulin analogues can be fully or partially offset by savings from averted costs of hypoglycaemia and other diabetes-associated complications [47–51].

Biosimilars are a potential way forward to reduce the cost of long-acting insulin analogues building on the appreciable price reductions seen with biosimilars to treat rheumatoid arthritis [52–56]. In addition, a number of published studies have now demonstrated similar effectiveness and safety between the originator and biosimilar long-acting insulin analogues [57–61]. However, potential savings from biosimilar insulin glargine can be limited in practice, potentially accentuated by the dominance of three companies currently controlling 96% of the global insulin market by volume and 99% by value discouraging competition [36, 46]. We have seen this in the United Kingdom with limited price differences with Semglee® (biosimilar insulin glargine 100 IU/ml) currently priced only 20% below the originator price and only 15% below the price of Abasaglar® (another biosimilar insulin glargine) [62]. Alongside this, there are concerns with increased rates of hypoglycaemia if patients are switched between different formulations of insulin glargine 100 IU/ml with different devices without full patient education [63–65]. These limited price differences were also seen in a recent study by Ewen et al. where median biosimilar prices for insulin glargine across lower- and middle-income (LMIC) countries ranged from 2% to 25% below originator prices, and sometimes biosimilar prices were higher in private pharmacies [35]. However, this was not the case in a recent study in Bangladesh with appreciable price reductions for biosimilar insulin glargine enhanced by competition between manufacturers [37]. WHO prequalification should also enhance competition leading to lower prices for biosimilar long-acting insulin analogues [66]. This is welcomed since limited price reductions for the biosimilar analogues can easily be matched by the originator company to protect its market given envisaged low cost of goods apart from insulin detemir [46, 67]. As a result, the attractiveness of the European long-acting insulin analogue market for biosimilar manufacturers could be potentially reduced, and thereby, possible competition leading to lower prices.

Concerns regarding the different devices between the originator and biosimilars may well have resulted in the low use of insulin glargine biosimilars (9%) among diabetologists in the UK in 2017 further limiting the attractiveness of the long-acting insulin biosimilar market [68]. However, this is not universal with some commissioning groups in England achieving utilisation rates of 53.3% for biosimilar insulin glargine in December 2018 versus total insulin glargine [69].

Other activities to reduce the attractiveness of the long-acting insulin analogue market for biosimilar manufacturers include the originator company launching more concentrated patented formulations to enhance patient convenience and potentially further reduce rates of hypoglycaemia, i.e., a 300 IU/ml formulation of insulin glargine (Gla-300) [41, 70–75]. Having said this, other researchers have found no difference in effectiveness between the different strengths of insulin glargine and concerns with possible underdosing with the 300 IU/ml formulation [76]. These "evergreening" activities by the originator company to preserve its market share in the face of potential competition are similar to the launch of different devices for the treatment of asthma to try and improve adherence rates and protect sales as well as the development of longer-acting oral formulations and intramuscular formulations of atypical antipsychotics to improve compliance and reduce recurrences [77–80]. Such company activities are also seen in other disease areas. These include the launch of esomeprazole versus omeprazole, escitalopram versus citalopram, and pregabalin versus gabapentin [81–85]. We are aware of prescribing restrictions for Gla-300 in some of the European countries [86]; however, this is not universal, and sales are growing especially with publications suggesting improved cost-effectiveness versus 100 IU/ml formulations [41].

Consequently, in view of the current controversies and issues surrounding the use of long-acting insulin analogues as well as the biosimilars, we believe that there is a need to assess current utilisation and expenditure patterns for the

long-acting insulin analogues including biosimilars across Europe and the rationale for any patterns seen. The findings can be used by health authorities across Europe to enhance the use of biosimilar long-acting insulin analogues where pertinent to limit the budget impact of increasing the number of patients with diabetes across Europe including those requiring insulins. This will be important to preserve universal access especially post-COVID-19 with its resultant impact on available resources coupled with increases in patients with NCDs and their complications as a result of lockdown and other measures [87, 88].

2. Materials and Methods

We included a range of European countries incorporating both Western as well as Central and Eastern European (CEE) countries covering a range of geographies, epidemiology, and economic power in terms of GDP per population. This is similar to other studies conducted across Europe [89–91]. We particularly wanted to include CEE countries since there has been appreciably lower use of biologicals in these countries versus Western European countries due to issues of cost and affordability [92–96].

We typically used reimbursed data from heath authority and health insurance company databases from 2014 or later until 2020 when assessing utilisation and pricing patterns for the different insulin preparations. These were supplied by coauthors in each country since the content of these databases are typically not publicly available. This is different to studies by Beran et al. and Ewen and colleagues who use a wide variety of sources when computing cost data [35, 46, 97]. This is because the perspective of this paper is a health authority one; consequently, we concentrated on their databases. These databases are also seen as robust, and they are regularly audited [89, 98, 99]. Consequently, health authority data is seen as a reliable source for comparing and contrasting utilisation and expenditure patterns across countries [98]. We principally centred on insulin glargine as this is the only biosimilar insulin currently available across Europe at the time of the study.

Utilisation data was broken down into Defined Daily Doses (DDDs). This is because DDDs are seen as a key standard for comparing utilisation patterns across countries especially if there are different pack sizes and strengths between countries [100–102]. We acknowledge that some published studies have suggested that DDDs may understate the amount of insulin that patients prescribed 300 IU/ml insulin glargine receive versus those prescribed 100 IU/ml formulation; however, others have not seen this [74, 103]. We have used this approach before in multiple publications when assessing utilisation and expenditure patterns across disease areas and countries [89–91, 104–107].

Expenditure data was principally reimbursed data since, as mentioned, the perspective of this paper is a health authority one. In a minority of situations, we also used total expenditure where it proved difficult to break expenditures down into the individual components. This again is in line with previous publications [89–91, 104–108]. Expenditure data remained where relevant in the local currency as we were principally interested in percentage differences in costs over time between the originator and biosimilars, as well as price reductions over time, rather than absolute levels and without any influence from currency fluctuations.

Utilisation and expenditure data on insulin glargine was further broken down into the different formulations, e.g., different 100 IU/ml formulations, as well as for the 300 IU/ml formulation (Gla-300) since, as mentioned, we were aware that the parent company had been switching its promotional activities towards the patented 300 IU/ml formulation in recent years to protect its market and help deter biosimilar manufacturers.

We combined the information from over 20 European countries and regions to provide the following datasets for comparisons:

(i) Utilisation of long-acting insulin analogues as a percentage of total insulin utilisation based on DDDs

(ii) Expenditure on long-acting insulin analogues as a percentage of total insulin expenditure based on local currencies

(iii) Utilisation of biosimilar insulin glargine (100 IU/ml) as a percentage of total insulin glargine (100 IU/ml) again based on DDDs

(iv) Utilisation of insulin glargine 300 IU/ml as a percentage of total insulin glargine again based on DDDs

(v) Cost/DDD for both originator and biosimilar insulin glargine (100 IU/ml) over time with the data subsequently used to track price changes over time

The information on utilisation and expenditure patterns was supplemented by feedback from the coauthors regarding the patterns seen in their countries to provide future guidance. The senior-level coauthors also contributed to discussions regarding potential next steps to enhance future savings from increased utilisation of biosimilars based on their considerable experience in this area. We have adopted similar approaches before to provide future guidance in this and other areas [55, 89, 104, 109–113].

We did not seek ethical approval as we were not dealing with patients. This is in line with national legislation and institutional guidelines as well as multiple previous papers conducted by the coauthors in other disease areas and situations [89, 104, 105, 114–116].

3. Results

3.1. Utilisation for the Different Insulin Preparations Over Time. There has been growing utilisation for long-acting insulin analogues over time among both Western and CEE countries, with no obvious difference in the rates of utilisation and increase between Western and CEE countries (Figure 1). This reflects the growing recognition of the role and value of long-acting insulin analogues in the management of patients with diabetes mellitus across Europe coupled with their increasing promotion.

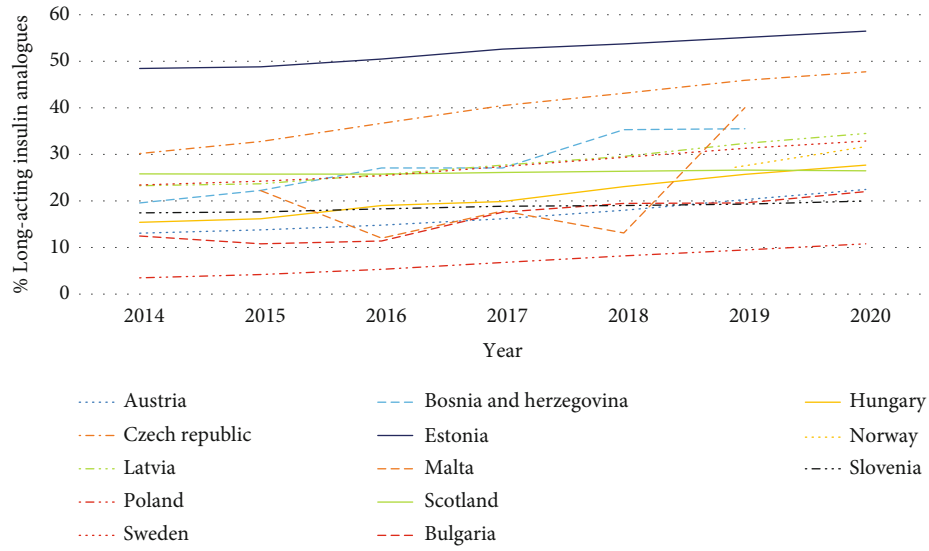

Figure 1: Utilisation of long-acting insulin analogues as a percentage of total insulins over time across Europe (DDD based).

The greatest utilisation of long-acting insulin analogues in recent years was seen in Estonia (56.5% of total insulins), Czech Republic (47.8%), and Malta (40.0%). There was also considerable prescribing of long-acting insulin analogues in Catalonia in recent years reaching 55.2% of total insulins in 2020 (not shown in Figure 1). However, the variable use of long-acting insulin analogues in Malta reflects procurement practices for that year; consequently, rates can be flexible between the years with implications for accuracy for any one year.

The least change in the prescribing patterns for long-acting insulin analogues was seen in Scotland (2.7% increase over time), with the greatest change seen in Poland (210.6% increase over time), but from a low base. In Poland, this may reflect a more cautious attitude towards long-acting insulin analogues coupled with issues of affordability. There was also a more cautious approach to the prescribing of long-acting insulin analogues in Slovenia, with similar prescribing rates over time (10.7% increase between 2014 and 2019). This may again reflect issues of value and affordability; however, more research is needed before we can say anything with certainty.

The stable utilisation of long-acting insulin analogues in Scotland in recent years (Figure 1) may well reflect adherence to the advice from NHS Scotland that patients in Scotland should ideally be started on human intermediate acting insulins, with long-acting insulin analogues only considered based on an assessment of a patient's hypoglycaemic risk. Adherence to agreed guidance is enhanced by regular monitoring of physicians' prescribing of long-acting insulin analogues versus other insulin preparations in Scotland [117]. We have seen monitoring of advice increase adherence rates to prescribed guidance in other disease areas in Scotland [83, 84, 118].

3.2. Expenditure for the Different Insulin Preparations Over Time. The increasing use of long-acting insulin analogues as a percentage of total insulins (Figure 1) was also reflected in similar changes in their expenditure compared with total expenditure on insulins (Figure 2).

Variations ranged from a slight fall in Romania and Slovenia over time with the cost/DDD for originator insulin glargine 100 IU/ml falling by 20.3% over time in Slovenia (Table 1) to a limited change in overall expenditure in Malta with the cost/DDD falling by 61.3% during the study period (Table 1). This compares with an appreciable increase in expenditure of long-acting insulin analogues in Kosovo over time but from a low base.

Increasing expenditure on long-acting insulins in Kosovo in recent years again reflects perceptions of improved patient convenience and outcomes versus standard insulins such as NPH insulins. There is a similar situation in Hungary with expenditure on long-acting insulins reaching 53.7% of total expenditure in recent years, similar to high expenditure rates in Estonia (63% in 2020), the Czech Republic (62.4%), and Latvia (45.5%). There was also appreciable expenditure on long-acting insulin analogues in Catalonia currently at 63.2% of total insulin expenditure (not shown).

The relatively high expenditure on long-acting insulins in Romania in recent years again reflects successful marketing by the originator companies with insulin glargine being one of the top selling medicines in Romania in recent years joined recently by insulin detemir.

3.3. Utilisation of Insulin Glargine including Biosimilar 100 IU/ml and 300 IU/ml (Gla-300). There has also been considerable variation in the use of biosimilar insulin glargine (100 IU/ml) versus total insulin glargine across Europe (Figure 3). This reflects a number of differences between countries in terms of switching of prescribing of insulin glargine from 100 IU/ml to patented 300 IU/ml (Gla-300) as well as activities of the originator company to lower its price to make the market less attractive for biosimilars.

Currently, no biosimilar insulin glargine is marketed in Albania, Austria, or Latvia. This may reflect increasing utilisation of Gla-300 in recent years rising to 45.3%, 47.7%, and

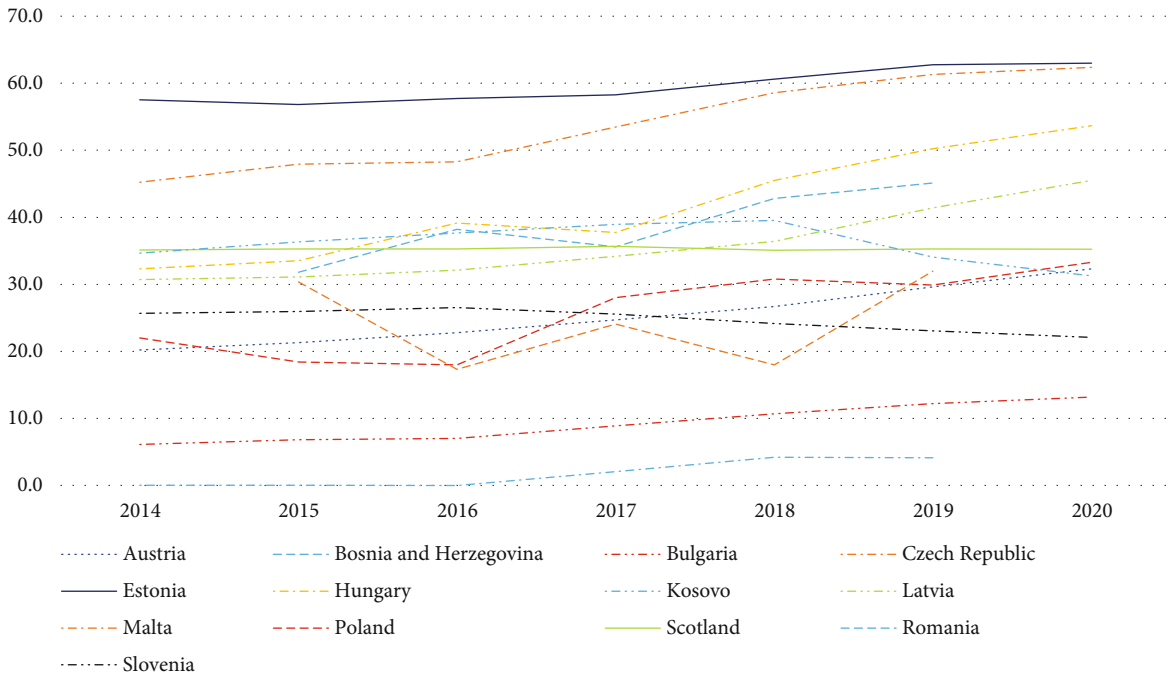

Figure 2: Expenditure on long-acting insulin analogues as a percentage of total insulin expenditure over time among European countries.

51.4%, respectively, of total insulin glargine in these countries as a result of commercial and other activities (Figure 4). This coupled with reduced prescribing generally of insulin glargine (Latvia), and price reductions of the originator over time (Albania and Latvia) (Table 1) appear to have made the 100 IU/ml biosimilar market unattractive in these countries. This is despite insulin glargine being the predominant long-acting insulin analogue prescribed in Albania in recent years, rising to 81.1% of total long-acting insulin analogues (DDD basis) prescribed.

There is also currently no biosimilar insulin glargine imported into Kosovo due to a number of issues including concerns with their effectiveness and safety versus the originator, and currently there is no biosimilar insulin glargine prescribed in Malta despite very limited use of Gla-300 (Figure 4). This probably reflects the considerable price reduction by the originator company making this market unattractive to biosimilar manufacturers (61.3%, Table 1). Similarly, whilst insulin glargine biosimilar has recently been reimbursed in Romania (Abasaglar® 100), its uptake to date has been very limited (not shown) due to ongoing pricing and reimbursement policies coupled with limited physician incentives to preferentially prescribe biosimilars alongside no copayment issues for patients.

There was also very limited utilisation of insulin glargine biosimilars in Estonia, contrasting with their growing utilisation in Lithuania as another key member of the Baltic States. This again probably reflects the originator company switching promotional activities to patented Gla-300 in Estonia to reduce biosimilar competition, with utilisation of Gla-300 growing to 55.4% of total insulin glargine in 2020 (Figure 4). In addition, the originator company dropping its price by 24.9% over time (Table 1) resulting in limited price differences in recent years between the originator and biosimilars (2.1%-7.1%).

Low and constant utilisation of biosimilar insulin glargine in Bulgaria again reflects continued marketing activities by the originator company coupled with currently a lack of physician incentives to preferentially prescribe biosimilars alongside limited price difference in practice between the originator and the biosimilar (Table 1), with both reducing their prices over time.

Low utilisation of insulin glargine biosimilars in Norway also potentially reflects limited price differences between the originator and biosimilar in recent years (Table 1) coupled with growing utilisation of Gla-300 (Figure 4). This contrasts with Sweden which has the highest biosimilar use among the studied European countries (Figure 3) despite growing use of Gla-300 (Figure 4). This is probably due to a tradition of prescribing of multiple source medicines with compulsory generic substitution in Sweden coupled with ongoing initiatives to enhance the quality and efficiency of prescribing including enhancing the prescribing of biosimilars [55, 106, 119, 120]. Ongoing initiatives also include devolving budgets locally to enhance the focus of ambulatory care physicians on prescribing efficiency.

The situation in Lithuania contrasts with the other Baltic countries as there has been growing utilisation of biosimilar insulin glargine as a percentage of all insulin glargine 100 IU/ml in recent years, reaching 26.5% of total insulin glargine 100 IU/ml in 2020 (Figure 3). This reflects the fact that all long-acting insulin analogues are in the same reference price group with patients covering the additional costs themselves for a more expensive medicine [121, 122]. Having said this, utilisation of the 100 IU/ml formulation has been moderated in recent years in Lithuania by increasing

Table 1: Changes in differences between prices for the originator and biosimilar insulin glargine 100 IU/ml across Europe in recent years (based on local costs/DDD).

(a)

	Albania	Austria	B & H	Bulgaria	Catalonia (Spain)
% difference originator vs. biosimilar price					
Launch of the biosimilar	Not applicable	Not applicable	No difference	4.7%	30.0%
Latest difference	Not applicable	Not applicable	7.9%	5.7%	Similar
% price change over time (from 2014/2015 to 2020)					
Originator	-32.0%	No change	-11.3%	-10.8%	-23.1%
Biosimilar	Not applicable	Not applicable	-17.1%	-11.7%	No change

(b)

	Czech Republic	Estonia	Hungary	Italy	Latvia	Lithuania
% difference originator vs. biosimilar price						
Launch of the biosimilar	17.1%	16.4%	28.2%	Not recorded	Not applicable	12.3%
Latest difference	Similar	7.1%	1.6%	31.6%	Not applicable	Similar
% price change over time (from 2014/2015 to 2020)						
Originator	-25.5%	-24.9%	-21.2%	52.3%	-14.4%	-21.1%
Biosimilar	-7.7%	Stable	1.2%	Not recorded	Not applicable	-6.8%

(c)

	Malta	Norway	Poland	Scotland	Slovenia	Sweden
% difference originator vs. biosimilar price						
Launch of the biosimilar	Not applicable	12.1%	24.7%	18.1%	22.9%	13.6%
Latest difference	Not applicable	5.9%	0.2%	7.5%	9.9%	0.6%
% price change over time (from 2014/2015 to 2020)						
Originator	-61.3%	-3.6%	-31.1%	-9.0%	-20.3%	-12.7%
Biosimilar	Not applicable	2.1%	-6.5%	No change	No change	-1.4%

utilisation of Gla-300, rising to 39.0% of all insulin glargine in early 2020 (Figure 4) coupled with price reductions by the originator (21.1% between 2015 and 2020) to limit any copayment differences.

There has also been growing utilisation of insulin glargine biosimilars in Bosnia and Herzegovina (B & H), but from a low base with the state agency recently encouraging physicians to prescribe biosimilars for new patients where possible, with physicians generally following national guidelines in B & H [108, 123]. Greater growth though is hampered by high utilisation of Gla-300, reaching 52.1% of all insulin glargine use in 2019 (Figure 4), and the originator dropping its price to reduce any resultant price differential (Table 1).

The growth in the utilisation of the biosimilar in Hungary is also welcomed as this was not the case with biosimilars for infliximab and rituximab [124, 125]. However, there are now ongoing reforms in Hungary to encourage physicians to start patients on the least expensive biosimilar as well as the reference pricing system with patients required to fund the difference in prices between the originator and any biosimilar themselves [126]. Having said this, utilisation of biosimilar insulin glargine in Hungary is again adversely affected by the originator dropping its price over time (Table 1) coupled with increasing use of Gla-300 reaching 58% of total insulin glargine in recent years (Figure 4).

The growth in the prescribing of biosimilar 100 IU/ml insulin glargine in Italy in recent years (Figure 3) probably reflects ongoing regional and national demand-side measures to enhance the prescribing of biosimilars given some of the price differences seen including for biosimilar insulin glargine (Table 1) and the need to conserve resources [127, 128]. However, greater utilisation of biosimilar insulin glargine may again be hampered by growing utilisation of Gla-300 in Italy in recent years (Figure 4).

We are also seeing growing utilisation of biosimilar insulin glargine in Scotland. However, growth is limited by concerns with switching between the originator and biosimilar 100 IU/ml insulin glargine, with physicians requesting to prescribe by brand name [64, 65]. This works in the UK with community pharmacists not allowed to substitute an originator with a generic without physician approval [80, 129]. Having said this, there are traditionally very high rates of INN prescribing in Scotland [83, 84, 118]. There is currently

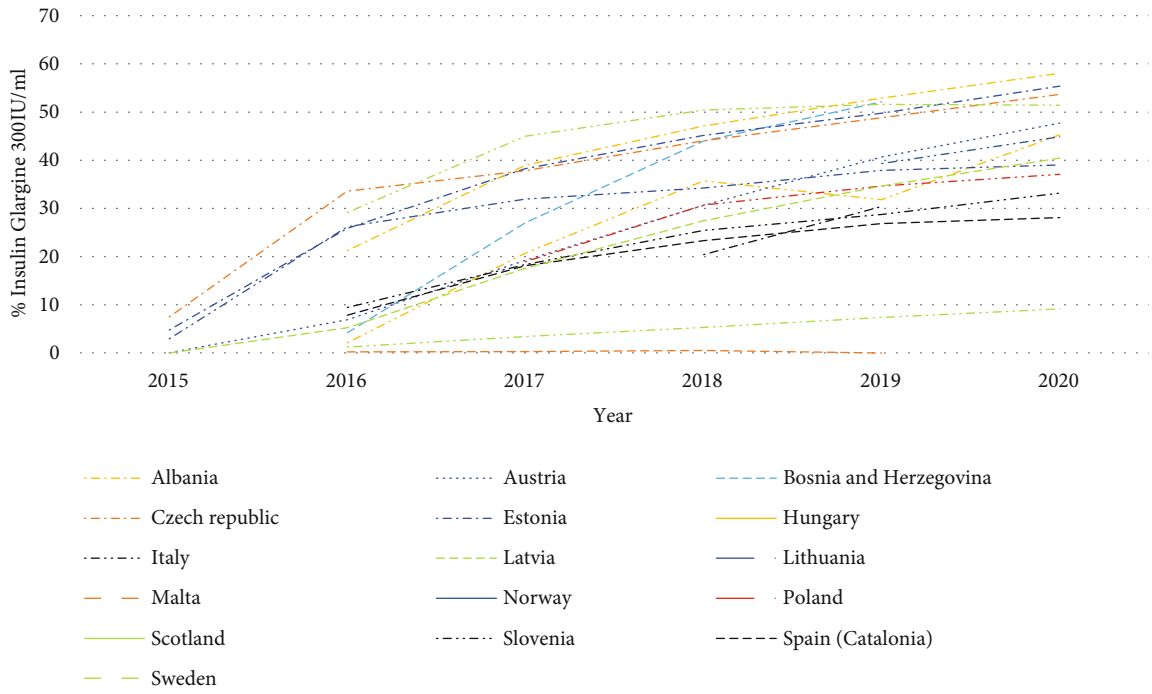

Figure 3: Utilisation of insulin glargine biosimilar (100 IU/ml) as a % of total insulin glargine 100 IU/ml (DDD based) over time across Europe.

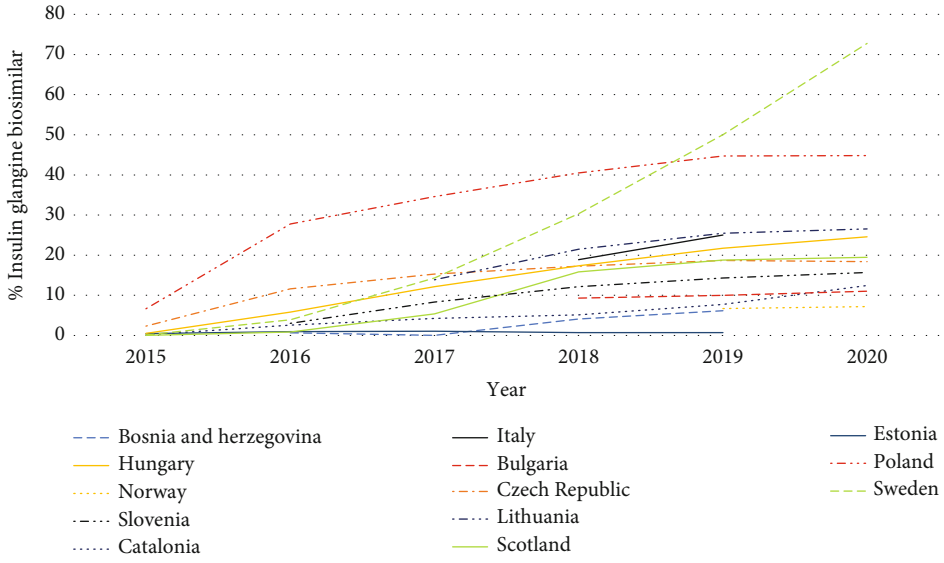

Figure 4: Utilisation of insulin glargine 300 IU/ml (Gla-300) as a % of total insulin glargine (DDD based) across Europe over time

low use of Gla-300 in Scotland as a result of ongoing prescribing guidance to limit its use enhanced by concerns that patients may inadvertently over dose [86].

The appreciably higher utilisation of biosimilar insulin glargine in Poland in recent years compared with a number of other CEE countries (Figure 3) may well be facilitated by a flat reimbursement rate with patients paying the price difference for a more expensive originator [126, 130]. Alongside this, the Ministry of Health and the National Health Insurance Fund in Poland are both looking to encourage the use of biosimilars to save resources especially as Poland is a leading producer of biosimilars in Europe [130, 131]. However, their prescribing is also hampered by growing utilisation of Gla-300 reaching 37.1% of total insulin glargine by early 2020 (Figure 4).

Prices are also now similar between the biosimilar insulin glargine and the originator in the Czech Republic potentially impacting on its use following a fall in originator prices (25.5%) and also biosimilar prices (7.7%) (Table 1). As a result, there is limited use of biosimilars despite growing

Educational initiatives

(i) Instigate programmes that educate patients where pertinent regarding similar effectiveness and safety between the originator and biosimilar insulin glargine. This includes actively disseminating the findings from previous and current studies including studies with real-world data

(ii) Instigate/help with additional research regarding the potential savings/cost-effectiveness from increasing use of biosimilar insulin glargine—building on current studies, with potential savings used to enhance either greater availability and use of long-acting insulin analogues in suitable patients with rising prevalence rates; alternatively, increase the number of professionals available to improve the care of patients with diabetes requiring insulin with the savings made

(iii) Alongside this, work with patients to ensure they are familiar with the different pens/devices where this exists in cases where switching between unfamiliar devices may cause confusion—the objective being to minimise any potential for hypoglycaemia

(iv) Concurrently, work with patient organisations to facilitate greater use of biosimilar insulin glargine especially where resources/-copayments are an issue and help with patient education to enhance optimal use of available devices where pertinent [132]

(v) Increased competition with greater availability of biosimilars should help to further lower prices benefitting all key stakeholder groups

Other suggested activities

(i) Encourage greater discounts from companies to enhance the use of biosimilar insulin glargine at lower costs—building on examples with oral generics [122, 133, 134]. This includes helping to cover the costs of any educational activities needed to enhance familiarity with different devices to minimise potential hypoglycaemia

(ii) Potential activities to encourage increased prescribing of biosimilars (and hence competition) could include the following:

(a) Introducing/progress annual procurement practices—with preference given to biosimilar companies

(b) Consider potentially delisting originator insulin glargine 100 IU/ml from reimbursement and formulary lists and/or only authorising reimbursement for biosimilars—building on successes in other disease areas and situations [118, 135]

(c) Introduce target prescribing goals for biosimilars for both new and existing patients with diabetes requiring insulin for their management—and where necessary provide additional educational support (with the help of patient organisations and other healthcare professionals)

(d) Introduce prescribing restrictions/guidance for still patented Gla-300 IU/ml to further enhance the market attractiveness for 100 IU/ml formulations—similar to the situation in Scotland [86]. This builds on the successful introduction of prescribing restrictions in other disease areas across Europe [91, 136–138]

(iii) Potentially form consortia surrounding the purchasing of biosimilar insulin glargine to encourage greater competition among manufacturers to reduce the current monopoly of insulin availability from the three leading pharmaceutical companies. This can build on current Pan-European consortia activities [139–141]

(iv) Look to increase European production of biosimilar insulin glargine building on current activities in countries such as Poland and Malaysia [130, 131, 142]. Lower prices for biosimilar insulin glargine should help lower- and middle-income countries struggling to fund long-acting insulin analogues due to issues of affordability [35, 143, 144]

Box 1: Potential activities among health authorities to enhance the prescribing and dispensing of biosimilar insulin glargine.

utilisation of long-acting insulin analogues in the Czech Republic reaching 47.8% of total insulins in 2020 (Figure 1). There are current restrictions regarding the prescribing of long-acting insulin analogues in the Czech Republic, with long-acting insulin analogues only reimbursed if current treatment regimens fail to achieve target HbA1c levels below 60 mmol/mol or if patients prescribed human insulins repeatedly experience severe hypoglycaemia. Concomitant with this, treatment with long-acting insulin analogues should no longer be reimbursed unless there is a demonstrable improvement in the patient's HbA1c levels within three months of initiation, i.e., a reduction by at least 10%, or significant reduction in the incidence of hypoglycaemia. However, there is currently variable follow-up of these restrictions in practice.

3.4. Potential Strategies to Enhance the Prescribing of Biosimilar Insulin Glargine. Box 1 contains a number of potential strategies to enhance the utilisation of biosimilar long-acting insulin analogues in Europe. This builds on currently variable utilisation of biosimilar insulin glargine across Europe. This is seen as essential to stimulate the market for the benefit of key stakeholders in the future.

4. Discussion

We believe this is the most comprehensive study to date to explore current utilisation and expenditure patterns for different insulin preparations, with a particular focus on insulin glargine and its biosimilars, across Europe. There has typically been increasing utilisation of long-acting insulin analogues across Europe despite their higher price (Figure 1), reflecting perceived patient benefits in terms or reduced hypoglycaemia and greater convenience. This increased use is seen in both Western European and CEE countries demonstrating that affordability is not an issue unlike a number of lower- and middle-income countries [35, 143, 145]. Similar patterns were seen when evaluating changes in expenditure on long-acting insulin analogues as a percentage of total expenditure on insulins (Figure 2).

However, there are concerns with limited or no use of biosimilar insulin glargine in a number of European countries despite a number of studies showing no difference in effectiveness and safety between the originator and biosimilars [57–60] (Section 3.3). This is due to a number of factors including promotional efforts by the originator company to change prescriptions to patented Gla-300 with limited

demand-side initiatives from health authorities to discourage this with the exception of Scotland with its prescribing suggestions to limit the use of Gla-300 [86]. In addition, the company lowering the price of the originator often to near or similar to biosimilar prices (Table 1), which coupled with concerns with different devices between the different insulin glargine 100 IU/ml formulations in some markets, has further limited biosimilar use. Alongside this, the continued domination of the insulin market by three manufacturers discourages competition [36, 46].

These issues need to be addressed to enhance the attractiveness of the biosimilar long-acting insulin analogue market, especially with the potential for low cost of goods [46, 67]. We have seen with biosimilars for managing patients with inflammatory diseases such as rheumatoid arthritis that increased competition can lead to low prices for biosimilars [52, 54, 56, 146], and this should be encouraged for long-acting insulin analogues in Europe. Failure to do so will limit the attractiveness of this market to other manufacturers of biosimilar insulin glargine as well as potential manufacturers of other long-acting insulin analogues as these compounds lose their patents. This will be to the detriment of key stakeholder groups especially given rising rates on diabetes across Europe [9] and growing resource issues post-COVID-19. Box 1 contains a number of activities that European health authorities can instigate to increase competition and subsequent prescribing of biosimilar long-acting insulin analogues, building on demand-side and other measures in other disease areas, and we will be monitoring these in the future.

We are aware of a number of limitations with this study. These include the fact that we did not include all European countries. However, we do not believe that increasing the number of European countries would have appreciably altered our findings. In addition, we only used health authority and health insurance company databases. This was deliberate for the reasons stated. Thirdly, we used DDDs for documenting and analysing utilisation data aware though of the potential problems with Gla-300. This was again deliberate for the reasons stated. Finally, we did not undertake an in-depth analysis of the rationale behind the trends seen in each country. However, feedback was based on the experience of senior-level coauthors in each country. Consequently, we believe our findings and suggestions are robust providing future direction.

5. Conclusion

In conclusion, we have seen growing use of long-acting insulin analogues across Europe reflecting their perceived benefits with improving compliance and reducing hypoglycaemia. However, there are concerns with limited or no use of biosimilars of long-acting insulin analogues in a number of European countries due to a number of factors. These include promotional efforts by the originator company and price reductions matching those of biosimilar manufacturers. These issues need to be addressed to enhance the utilisation of biosimilars in the future to the benefit of all key stakeholder groups.

Data Availability

The content of health authority and health insurance company databases is typically confidential. However, reasonable requests for information will be considered and actioned where possible. The coauthors from the various European countries have been responsible for the content and accuracy of the information they have provided.

Disclosure

The authors are totally responsible for the views expressed in this paper, and they do not necessarily represent the decisions, policy, or views of the World Health Organization.

Conflicts of Interest

The authors have no relevant conflicts of interest to declare. However, a number of the coauthors work for health authorities or are advisers to them.

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Review Article

COVID-19 Vaccine, TRIPS, and Global Health Diplomacy: India's Role at the WTO Platform

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In light of the devastation caused by COVID-19, the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and vaccine research and development (R&D) have been occupying a prominent position in the field of global health diplomacy (GHD). Most countries, international organizations, and charitable organizations have been engaged in the R&D of COVID-19 vaccines to ensure timely affordability and accessibility to all countries. Concomitantly, the World Trade Organization (WTO) provides some provisions and enforcements regarding copyrights, patents, trademarks, geographical indications, and industrial designs. Given these safeguards, it is considered that intellectual property rights (IPRs) have become major barriers to the affordability and accessibility of vaccines/medicines/technology, particularly to the developing/least developed countries. Realizing the gravity of the pandemic impact, as well as its huge population and size, India has elevated this issue in its global health diplomacy by submitting a joint proposal with South Africa to the World Trade Organization (WTO) for a temporary waiver of IPRs to ensure timely affordability and accessibility of COVID-19 medical products to all countries. However, the issue of the temporary waive off had become a geopolitical issue. Countries that used to claim per se as strong advocates of human rights, egalitarianism, and healthy democracy have opposed this proposal. In this contrasting milieu, this paper is aimed at examining how the TRIPS has become a barrier for developing countries' development and distribution of vaccines/technology; secondly, how India strategizes its role in the WTO in pursuant of its global health diplomacy? We conclude that the IPRs regime should not become a barrier to the accessibility/affordability of essential drugs and vaccines. To ensure access, India needs to get more engaged in GHD with all the involved global stakeholders to get strong support for their joint proposal. The developed countries that rejected/resisted the proposal can rethink their full support.

1. Introduction

In the context of COVID-19, the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) has been identified as one of the most significant barriers to vaccine and medicine affordability, particularly for developing and least developed countries. TRIPS is a hard law instrument that is enforceable and binding; it mandates patent protection for pharmaceutical products for up to 20 years, and any violations result in trade sanctions [1]. Apart from the lack of pharmaceutical research and development (R&D), patents on pharmaceutical products and processes and poverty used to become double whammies for third world countries. Given the monopolies over vaccine production, marketing and fixing the higher prices maximize profits by the multinational pharmaceutical and drug companies/developed countries. Global health diplomacy is an integral part of Indian foreign policy. Recognizing the urgency of the situation, India and South Africa have jointly submitted a draught request to the World Trade Organization (WTO) for a temporary waiver of intellectual property (IP) rights to make COVID-19 medications affordable and accessible to all. [2]. In this scenario, the main focus of this paper is to examine how the pharmaceutical TRIPS have become a barrier to the development and distribution of vaccines/technology to the poor countries. The paper also argues why the developed countries (advocates of health, democracy, egalitarianism, and protection of human rights) are refusing to support the temporary IP waiver proposal for the humanitarian cause. Even though international trade cooperation has suffered from geopolitical shifts and competition in the midst of the pandemic crisis, governments can align their trade and health policies to serve the global community by engaging in GHD [3].

Because of this COVID-19 pandemic and the consequent lack of vaccines/medicines, many developed countries are actively engaged in vaccine R&D. According to recent findings from a country pandemic risk exposure measurement model, the national risk management strategies in Italy and Spain have anticipated these needs [4]. On the contrary, public criticism in many developing nations has grown exponentially, as issues about the legitimacy of patents on life-saving vaccines have been raised. This has contributed to the call for modifications or amendments to the TRIPS, which many claims are too strongly favoring private and commercial rights and interest, and against public interests. However, developing countries such as India and South Africa, which are seen as the emerging leaders of third world countries, are concerned that TRIPS may prevent the patients from these countries' from accessing essential COVID-19 vaccines/medicines/technologies. Given this context, we conducted a review to examine how TRIPS has become a barrier to the development and distribution of vaccines/and technology in developing countries. Second, we looked at how India strategizes its involvement in the WTO through its global health diplomacy.

2. Methodology

A literature search was done in all the major databases, namely, PubMed, Web of Science, Scopus, and Google search engine for the terms "COVID-19" OR "COVID-19 Vaccine" OR "Trade-Related Aspects of Intellectual Property Rights (TRIPS)" OR "World Trade Organization" OR "Global Health Diplomacy" AND "India." All relevant titles were screened, and essential information was extracted in preparation for this review. A total of 40 full-text articles and eight other reports were reviewed, and the findings are discussed in three main sections, namely, (1) COVID-19 medical products and TRIPS, (2) COVID-19 Vaccine and TRIPS, and (3) Global Health Diplomacy: India's Role at the WTO Platform.

3. Results

3.1. COVID-19 Medical Products and TRIPS. The economic and social disruptions caused by the COVID-19 pandemic are devastating. Millions of people are at the risk of falling into extreme poverty. Globally, there have been 115,653,459 cases, including 2,571,823 deaths reported to WHO as of March 6, 2021 [5]. It had become a critical challenge for the developing and least developed countries where healthcare systems are not adequate to care for the affected people. With its great toll of lives and strain on the healthcare systems, COVID-19 has been a great challenge for such countries and even the developed countries. On December 2, 2020, WHO has published its official release of "Draft Landscape of COVID-19 Candidate vaccines 2020," which contained a total of 51 Candidate Vaccines in Clinical Evaluation with more additions coming in [6]. Treatments available for patients suffering from an active clinical form of the disease also remain scattered and without firm consensus on efficiency ranging from old antimalarial drug chloroquine [7] over convalescent plasma [8] up to novel targeted monoclonal antibodies [9]. Secondly, it had left indelible imprints on unemployment, poverty, hunger, undernourishment, etc. Thirdly, whatever the efforts are being made for vaccines R&D [10] that would likely remain beyond common people's reach, given the high prices of the same due to TRIPS. A number of studies have already proven that the most developed non-OECD South Asian countries confront significant impediments to the financial affordability of pharmaceuticals for the general public, even in the richest coastal and metropolitan districts of their major cities [11]. Now, how TRIPS is one of the major concerns for the availability of the medicines is the moot question in this context?

The intellectual property rights (IPRs) started taking place during the late 19th century, formally concretized in 1995. The IPRs are meant for protecting the creators/agencies' exclusive rights over the creation/s for a certain period. While the agreement establishes minimum standards for intellectual property right (IPRs) protection in the form of patents, trademarks, geographical indications, industrial designs, and the enforcement of those rights in all WTO member countries, it is primarily concerned with reducing distortions and impediments to international trade.

The TRIPS has been conceived very beneficial for society, particularly given the imposition of temporary monopolies and other limitations resulting from private IPRs [12,

13]. By putting legal protections in place and tackling piracy and counterfeiting through the IPs, the creation of new knowledge, innovation, and creativity is being encouraged. Therefore, the costs associated with the R&D can be retrieved, and remuneration would be earned. Matthews [14] argues that the IP regime not only stimulates domestic innovation but also promotes knowledge diffusion, technology transfer and licencing, and Foreign Direct Investment (FDI) to developing and least developed countries, thereby promoting trade and economic development in those countries. On the contrary, Sell and Prakash [1] have argued that the TRIPS has also been subjected to severe criticism since their inception. Recently, on October 16, 2020, during the WTO TRIPS Council meeting, nine WTO members, including the European Union, did not support the proposal though 100 countries showed support for the proposal. Though Canada became the first country worldwide to reform its domestic law to enhance developing countries' access to patented medicines [15], it did not support the IP waiver proposed by India and South Africa recently in October 2020. It was proposed that Canada should assist developing countries in their calls for greater access to existing pharmaceuticals and technologies, as well as access to new treatments and equipment. Furthermore, it is an excellent time for global solidarity, and Canada should take advantage of this chance to reassess its position on IP acquisition in relation to other domestic and international policy levers [16].

3.2. COVID-19 Vaccines and TRIPS. Since the introduction of research and development in the biological sciences, vaccines have been given a vital place and role in saving millions of lives each year. Vaccines are used to prepare the body's natural immune system to combat viruses and bacteria. On December 2, 2020, WHO published its official release of "Draft landscape of COVID-19 candidate vaccines 2020," which contains a list of 51 candidate vaccines in clinical evaluation [6]. Yet, we mentioned ongoing efforts to foster early marketing approvals by shortening phase III development duration, with the first global official launch in Russia [17] for emergency use authorization. However, it has not received fully marketing approval in Russia. Similar accelerated development pathways currently occur in the US, China, India, Germany, UK, and possibly Israel [18]. Against this backdrop, the COVID-19 vaccine R&D program has been ongoing at an unprecedented pace to make a preventable disease vaccine [19]. Even assuming this ends up with several agents of acceptable efficiency–toxicity profile, it remains an open-ended question of public acceptance of massive vaccination. Public opposition to such an epidemiological strategy to achieve herd immunity is notable globally, with a huge population of Pakistan being a convenient example [20].

Many scholars such as Thanh et al. [21] and Fau et al. [22] argued that soon after coronavirus detection in December 2019, the genetic sequencing of COVID-19 was published on January 11, 2020 which has necessitated an urgent international reciprocation to develop a preventive vaccine immediately. Schmidt [23] has reported in one of his opinions that about 80 companies, and institutes in 19 countries have been engaged in COVID-19 vaccine R&D. According to Thanh et al. in their report in the Coalition for Epidemic Preparedness Innovations (CEPI), in terms of R&D of COVID-19 vaccine from a geographical standpoint, North America covers 40%; Europe covers approximately 26%; and South America, Africa, Asia, and Australia collectively cover only 30%. These figures indicate that the developed countries monopolize the R&D of the vaccine.

International organizations have taken the lead in this direction and formed international alliances to expedite the R&D of vaccines. International organizations such as the World Bank, WHO, along with the Bill and Melinda Gates Foundation and other International NGOs, have raised a fund of US$ 8.1 billion and introduced the WHO COVAX plan for the fair and equitable distribution of an eventually licensed vaccine. CEPI has also created another fund of US$2 billion from the global partner for the fast-tracked research and clinical testing. Several countries like Belgium, Canada, Germany, Norway, the Netherlands, Switzerland, the UK, and charitable organizations like The Bill and Melinda Gates had contributed about US$ 915 and US$250 million, respectively, in support of CEPI research and public education support for COVID-19 vaccines [24]. In these times, where vaccine nationalism is on the drive due to the scarcity of vaccines, initially, the COVAX initiative is an instrument for a fairer global distribution [25]. Concomitantly, the Global Research Collaboration for Infectious Disease Preparedness (GLoPID-R) and the International Severe Acute Respiratory and Emerging Infection Consortium have been working toward COVID-19 research and eventual vaccine distribution. A virtual summit was organized with private and government representatives of 52 countries, including 35 heads of state from G7 and G20 nations, who supported the Global Alliance for Vaccines and Immunization (GAVI). For example, the European Commission had invested about €80 million in CureVac. Here, we must emphasize a crucial role in global health funding by a set of huge non-OECD actors nicknamed Emerging Markets. Notably, the five nations have been known under the acronym BRICS (Brazil, Russia, India, China, South Africa) or Emerging Markets Seven (EM7-Brazil, Russia, India, China, Mexico, Indonesia, Turkey) [26]. Real GDP growth rates among the EM7 remained substantially higher than G7 during the entire decade of the last global macroeconomic crisis, 2007-2016. Worldwide economic growth accelerating again in 2017 had roughly half of this growth being attributable to the EM7 and only one quarter to the G7 nations. Thus, the health sector's investment and their huge impact on the demand and supply of medical goods and services during the COVID-19 pandemic period shall play an inevitably colossal role. Furthermore, these long-term health expenditure trends are likely to become even more prominent as we approach the mid-2020s as per some prominent forecasts [27].

Some countries have been working in the direction of developing COVID-19 vaccines. The Canadian government pooled about CA$ 275 million for 96 vaccine research projects at Canadian companies and universities, along with a

commitment for CA$ 850 million to the WHO for COVID-19 vaccines and preparedness [28]. The Chinese government has been providing low-rate loans to vaccine companies and research institutes. It had also pledged on May 18 to provide about US$ 2 billion to the WHO for the latter's COVID-19 vaccine plans, as well as a US$ 1 billion loan to Latin America and the Caribbean countries to make its vaccine accessible [29]. France had committed a US$ 4.9 million investment in COVID-19 vaccine research undertaken by the CEPI. Germany committed to investing about €300 million investment in CureVac. Several countries like Belgium, Canada, Germany, Norway, the Netherlands, Switzerland, and the UK had contributed about US$ 915 for the COVID-19 vaccines. The other vaccines rolled out with more support from the EU, US, and the UK that are from the Pfizer/BioNTech, AstraZeneca, Moderna, and Johnson & Johnson in early 2021.

The US's federal agencies like Biomedical Advanced Research and Development Authority (BARDA) had announced that about US$ 1 billion would be invested in vaccines. An additional amount of US$ 4 billion would be spent on vaccine development with companies like Sanofi Pasteur and Regeneron. The "Operation Warp Speed" fast-track program announced that it would collaborate with seven businesses to produce COVID19 vaccines, including Johnson & Johnson, Moderna, Merck, Pfizer, and the University of Oxford in partnership with AstraZeneca [30].

From the above discussion, it is clear that most of the countries, international organizations, and charitable organizations engaged in the R&D of COVID vaccines are from the Western world. Currently, the TRIPS has been providing many IPs related to vaccines. TRIPS Article 7 explains the objectives in terms of protection and enforcement of the IPs as "the promotion of technological innovation," "the transfer and dissemination of technology" to the mutual advantage of both "producers and users of technological knowledge," and "social and economic welfare." Article 8 obligates the member countries to protect public health and nutrition and promote the public interests congruent to the TRIPS Agreement provisions [31]. Moreover, it is the fundamental responsibility of sovereign governments to protect their citizens' health and safety. The Article 73 of the TRIPS Agreement may justifiably be invoked to override IP protections because the pandemic constitutes an emergency in international relations within the meaning of Article 73 (b) [32].

Brooke and Sherris [33] had argued that the availability of vaccines, particularly in the low and middle-income countries, depends mainly on the prior evaluation by the developed countries/regions like the US or European drug regulatory agencies. Moreover, the pharmaceutical manufacturers used to receive a large chunk of revenues from the developed countries. Therefore, there are scanty financial incentives available if the same is not sold in the same markets. Additionally, poorer countries' health agencies used to take green signals from the developed countries before approving/not approving the new products in the market. Though this is an independent regulatory approval guaranteeing the safety and effectiveness before the use, under such paradigms, the TRIPS can still become a hurdle for the availability of vaccine technology.

Guimon et al. [34] stated that the pandemic will not recede until the COVID-19 vaccine is viewed as a global public good. Even the UNAIDS Executive Director Winnie Byanyima, in an open letter to the global pharmaceutical industry leaders, also called on the global pharma industry "to unlock the secrets to their COVID-19 vaccine technologies" to produce a cheap and accessible "People's Vaccine" and not a profit vaccine [35]. Even a working paper by WTO staff highlighted that the evidence-based debate on the scope and effect of the TRIPS policy options is a task more important today than ever [36].

4. Discussion

4.1. Global Health Diplomacy: India's Role at the WTO Platform. The outbreak of COVID-19 had taken place in December 2019 in Wuhan, China. Consequently, the same was declared a Public Health Emergency of International Concern (PHEIC) and "Pandemic" by the WHO on January 30 and March 11 in 2020, respectively [37]. Concomitantly, the WTO has also cautioned that the "Pandemic represents an unprecedented disruption to the global economy and world trade, as production and consumption are scaled back across the globe." The absence of vaccines/medicines for the ongoing pandemic became a more critical challenge for the entire globe. In this scenario, there was an overwhelming consensus for international collaboration to expedite vaccine development, manufacturing, a supply of effective medical technologies to ensure the protection of all patients across the globe. Even heads of several states urged the world leadership to treat the COVID-19 medical products as global public goods.

India has been known as the world's pharmacy, given its role in producing generic medicines [38]. Global health diplomacy has remained an important part of India's foreign policy. India has pursued the same at the peak of the pandemic. It had provided more than 150 countries with a wide range of medical and healthcare services, including medicines (hydroxychloroquine and paracetamol) and vaccines (Covishield and Covaxin). It has also collaborated with international organizations for vaccine R&D. It has contributed to the Global Alliance for Vaccines and Immunization (GAVI) [39].

In this backdrop, once again realizing the gravity of the situation, India and South Africa proposed a temporary waiver (IP/C/W/669) before the WTO's TRIPS Council as part of its global health diplomacy to expedite the development of medicines, vaccines, and diagnostics for prevention, containment, and treatment of COVID-19 [2]. Furthermore, the proposal casts a wide net, as practically any medical device required to diagnose, treat, or prevent COVID-19 could be eligible for such a waiver [40]. More than 350 civil society organizations and activists worldwide asked WTO member countries to support the Indian and South African joint proposal. Under the proposal's provisions, countries need to "waive off" the patents, copyrights, and other IPs not only for the products themselves but also for their

underlying technologies—without facing WTO charges or penalties for violation of international trade rules. To take the lead further, India and South Africa had argued before the Council for TRIPS that "Given the current global emergency, WTO Members must work together to ensure that intellectual property rights such as patents, industrial designs, copyright, and the protection of undisclosed information do not obstruct timely access to affordable medical products such as vaccines and medicines, or the scaling-up of research, development, manufacturing, and distribution of medical products essential to combat COVID-19" [2]. Many access-to-medicines movements were organized by patient activists, civil society, and health-right groups who stood up to governments' passivity in the past to resist the pharmaceutical industry's monopolies for HIV medicines and eventually succeeded in gaining patent relief. These movements have resulted in a significant decrease in the prices of HIV medicines (over $10,000/person/year) dropped by 99% over a decade by allowing generic drugs in developing countries. Currently, the COVID-19 pandemic situation also presents a similar situation as the pandemic has affected every nation. Though in the case of HIV epidemic, it affected the global south more than the north and thus the support came in from the rich nations in Western Europe and North America. However, in the current COVID-19 pandemic, the rich nations have been affected more, with more cases and deaths resulting in global competition, lack of solidarity, and nationalist movements in addressing the domestic economic and health crises. There is a lack of global leadership and international cooperation in the current scenario, with geopolitical shifts leaving behind the interests of the developing nations. Hence, in this current scenario, vaccine nationalism has taken precedence over global cooperation and solidarity. Therefore, if the TRIPS waiver proposal is approved, the access to essential COVID-19 medicines, technologies, and diagnostics will improve drastically [41].

The proposal was also supported by UNAIDS, UNITAID, MSF (Medecins Sans Frontieres), academics, researchers, and numerous civil society organizations [42]. The WHO wholeheartedly lent its support to the Indian and South African proposal. WHO chief had welcomed India and South Africa's proposal and said "To ease international & intellectual property agreements on #COVID19 vaccines, treatments & tests to make the tools available to all who need them at an affordable cost." The Indian leadership/health authorities realized that IPs are becoming barriers in the way of "scaling up production of test kit reagents, ventilator valves, N95 respirators, therapeutics, fluorescent proteins and other technologies used in the development of vaccines, etc." Moreover, the waive-off argument has been advanced, realizing that the existing flexibilities in the TRIPS Agreement are "not adequate to address the fast-changing landscape of COVID19." The fact that provisions under "compulsory licenses" are limited only to pharmaceutical products rather than the crucial medical devices required for combating the ongoing pandemic. The existing system became extremely onerous and time-consuming and of no practical use when exporters and importers have to comply with the existing provisions. In this backdrop, the joint proposal argued that the IP waiver has been very important, particularly for the developing countries with insufficient or no manufacturing capacities/finance for producing the vaccines/medicines [43]. However, these two are correlated but ultimately different problems. However, the financial resources are currently being raised for ensuring sufficient doses, but not the manufacturing capacities.

However, the proposal did not go through, given the rejection and lack of consensus among the developed countries. Rather, the WTO members have been divided into three groups. The first category including Chad, Tanzania, other African nations, Southeast Asia, and South American countries supported the proposal on behalf of the LDC countries and African Group. The second group of countries (China, Costa Rica, Chile, Columbia, Jamaica, El Salvador, Senegal, etc.) welcomed the proposal, but they did seek more clarifications. The third category comprises developed countries like Brazil, Canada, Norway, the UK, the US, Switzerland, and the EU, which outright rejected the proposal [42]. Chattu et al. have highlighted that though it is easy to talk of inequalities and inequities and include them in policies, and further added that, here is an opportunity for the world to show its solidarity for "Health For All" and nations should strive to find solutions to ensure equitable access to the COVID-19-related drugs, medical supplies, and vaccines [41].

From the above discussion, it becomes crystal clear that most vaccine R&D has been taking place in the developed countries' private and public institutions as it requires huge investments. However, at this juncture, the question is moot: which is more important, making money or saving a human life? This is weighing heavily on the minds of the public, especially in light of the ongoing critical issues of health and human security. Surprisingly, the developed countries, which are viewed as the main advocates of egalitarianism, democracy, health, and human rights by the global community, have not supported this humanitarian cause in the larger context. These 35 developed countries Australia, Brazil, Canada, Japan, Norway, Switzerland, the UK, the US, and the EU (27-member block) have rejected India's and South Africa's proposal. However, the other 100 nations have welcomed or fully supported it. This disagreement has resulted in rich vs. poor in the race of getting access to the COVID-19 medical equipment, treatment, and vaccines [43].

Have the TRIPS become a tool for the expansion of capitalism? Are these countries concerned about the 20 illnesses that can be prevented or treated, including COVID-19? If this is the case, why not put the question of returns, remuneration, profits, and so on to the side for the time being and focus on considerations, sensitivities, and humanitarian cause when whole humanity is suffering due to lack of access to COVID-19 vaccines and medicines?

To substantiate the above argument, it can be seen through the prism of deaths of millions of people due to infectious diseases every year. These diseases are perceived to be preventable or treatable. About 45% of deaths in Africa

and Southeast Asia have occurred due to infectious diseases [44]. The death toll is unprecedentedly and unacceptably high in developing and the least countries. In the context of African nations, which depend on the development aid from rich nations, it would be prudent for the Africa Centers for Disease Control and regional bodies to embrace global health diplomacy to strengthen their capacity for disease preparedness and response [45]. During this crisis, the developing countries, especially in Asia and Africa, need to realign themselves and strengthen their health systems. A recent systematic review by Chattu et al. has emphasized that African Union needs to refocus and prioritize the continent's health challenges by innovatively adapting the canons of GHD towards attracting more funding and developing collaborative partnerships with relevant actors in the global health domain [46]. Although, the health crisis is due to given interlinked factors such as lack of healthcare facilities, poverty, unemployment, lack of sanitation but the critical factor for the same is unaffordability [47], inaccessibility, monopolization of production, and distribution of vaccines/medicines in the backdrop of the agreement on TRIPS.

On public health, trade, human rights, and the environment, governments seem to have lost faith in the value of working together. As highlighted by Jones Bruce, in the absence of credible great-power leadership from the US or China, the "middle powers" such as France and Germany have led to coordinating health and economic responses. Though the concept of "middle powers" is imprecise and inchoate, it refers to nations from the top 20 economies and lack large scale military power (or chose not to have a lead role) and is energetic in diplomatic and multilateral affairs such as France, Canada, Netherlands, Sweden, Germany, and the United Kingdom which were trying to fill the gaps in the international leadership [48]. They have shown their commitment and dedication by raising over $14 billion for providing free vaccines through the Vaccine Alliance to the countries that cannot afford them [49]. As Gostin et al. highlight the complexity of global health coordination and universal access to the COVID-19 vaccine, global health law's role is very critical as it supports global solidarity and reaches agreements to secure equitable access [50]. Moreover, there is an immediate need for cooperation and collaboration, an understanding of shared responsibility, and critical aspects such as transparency, accountability, trust, and fairness to overcome this COVID-19 pandemic [51].

5. Conclusions

COVID-19 had left indelible imprints and taught us several lessons such as the importance of global solidarity, international cooperation, and focusing on inequities and inequalities exposed during the ongoing pandemic. Given the monopoly of private ownership over vaccines/medicines/-medical technology, the aspects of access and affordability to essential health care services will be compromised, violating the universal right to health. During this COVID-19 pandemic, the numerous facets of many healthcare systems' unpreparedness and fragile state were exposed. India, with its good infrastructure for pharmaceutical production and development, can become a hub for supplying generic medicines and essential medical equipment to the world, thereby improving access to the essential drugs, medicines, kits, and vaccines in many low- and middle-income countries (LMICs). There is a great need for cooperation and support from the developed nations to ensure the enjoyment of "right to health" by everyone. India must engage in global health diplomacy with a variety of global players to circumvent or obtain specific waivers for intellectual property rights (IP/IPRs) to safeguard the supply of life-saving and necessary pharmaceuticals and vaccines while maintaining equity and fairness. Every citizen has the right to health and human security. Therefore, the IP regime should not become a barrier to the availability and affordability of COVID-19 medical equipment and vaccinations. A large group of intellectuals, social activists, altruistic people, civil society organizations, nongovernmental organizations, international organizations, and other LMICs consider IPRs for COVID-19 essentials to be barriers during this pandemic. Hence, the countries that rejected the joint proposal of TRIPS waiver by India and South Africa should reconsider. Furthermore, those countries that claim to be strong supporters of human rights, egalitarianism, democracy, global health, and human security must rise to the occasion and lend their full support to India at the WTO for this great cause that prioritizes humanity over the business interests of the pharmaceutical industry.

Data Availability

The data presented in this study are available on request from the corresponding author.

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

VKC conceived the study and prepared the initial draft. BS, KK, and VKC did the literature search and data analysis. MJ reviewed the manuscript, and edited and provided critical comments. VKC edited the final version of the manuscript. All the authors have approved the final version before submission.

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