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Advanced therapeutic medicinal products (ATMPs) in Ischemic Stroke; novel therapeutic modalities from financial perspective

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ABSTRACT

Stroke, is accounting for more than 34% of total healthcare spending globally. Ischemic stroke (IS) accounts for 62.4% of incident stroke cases. IS-related direct medical expenditures place a considerable burden on healthcare system. The burden is more prominent in developing countries where limitations in insurance coverage is a big concern. It would be less challenging in developed countries, where costs are covered by third parties.

After introduction of advanced therapeutic medicinal products (ATMPs), a new line of treatments is proposed. Although the high prices of these treatments may cause financial concerns, they have encouraged scientists and provided acceptable results in a way that makes investment in this area reasonable for health experts. All ATMP-based therapies used in clinical trials for the treatment of IS are stem-cell-based or stem-cell-derivatives. The cost of stem-cell-based therapies are considerable like other alternative medical settings, e.g., thrombolysis and thrombectomy. However, the considerable recovery after prescription of ATMPs is expected to be cost-effective. Furthermore, various gene therapy approaches for the treatment of IS have been proposed. However, none has been qualified for clinical studies yet. If such a procedure is introduced in near future, it does not necessarily guarantee that these innovative treatments would be offered to the patients. Application of ATMPs have many challenges particularly in developing countries. This is primarily related to exorbitant expenditures. Despite these challenges, the insurance systems in developed-countries supports stem-cell therapies as novel treatments. Significant improvements in the insurance systems of both developing and developed countries are necessary.

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Abbreviations

IS, Ischemic stroke; ATMPs, After introduction of advanced therapeutic medicinal products; QALY, Quality-adjusted life-year; WHO, World health organization; BMMNCs, Bone marrow mononuclear cells; BMSCs, Bone marrow mesenchymal stem; iPSCs, induced pluripotent stem cells; MSCs, Mesenchymal stem cells; AAVs, Adeno-associated viruses; LVs, Lentiviruses.

Introduction

Stroke is known as the second leading cause of death, globally [1, 2]. On a worldwide scale, stroke accounts for around 34% of all health-related expenditures. Stroke seems to be a major burden on both developing and developed countries [3]. In 2016, the entire cost of stroke in the United States was estimated at around 49.8 billion USD [4], whereas the annual health budge was 3.1 trillion USD [5]. It means that stroke costs accounted for 1.6 percent of total health spending. This is while the estimated cost of stroke in a developing country, Iran, in 2018 was evaluated to be about 369 million USD [6], accounting for around 2.7 percent of total healthcare expenditure (13.58 billion USD) [7].

Ischemic stroke (IS) accounts for 62.4 percent of all incident stroke cases worldwide [8]. Costs of IS might be direct or indirect. Direct costs of IS include both medical and non-medical expenses. Medical expenses consist of acute IS care and rehabilitation charges [9]. In the acute phase, patients are considered to benefit from both thrombolysis with a tissue-plasminogen activator (t-PA), the only approved pharmacological therapy that must be taken within 4.5 hours of the beginning of symptoms, and mechanical thrombectomy. These procedures increase quality-adjusted life-year (QALY) and are essential components of acute IS therapy [10-13]. Prices of hospitalization, cardiology-related investigations, and rehabilitation services are all other elements of IS acute care costs. Nonmedical direct costs include relocation fees for care providers and patients, and the cost of making modifications to one's diet, residence, and vehicles [9]. Indirect costs are defined as productivity losses caused by illnesses or deaths, including diminished performance related to hospitalization time [14].

During the last few decades, a new category of treatment has developed. Advanced therapeutic medicinal products (ATMPs) seem to be promising treatments for a variety of diseases. ATMPs include gene therapy, cell therapy, and tissue engineering. Despite the significant outcomes, ATMPs are still challenging in terms of costs [15]. In both developing and developed countries, direct medical expenditures of IS are a financial burden on patients and the healthcare system, and thus the adoption of ATMPs may incur additional costs. In this study, the authors will review the existing data on the preparedness of insurance systems to implement ATMPs in the treatment of IS in both developing and developed countries. To minimize the probability of financial value bias, all values are converted to 2022 USD using the initial reported value [16].

Direct medical costs of IS in developing countries

Direct medical expenditures in developing countries vary by country; nonetheless, they range between 497 USD to 10,229 USD, excluding thrombolysis and thrombectomy [9]. The aforementioned procedures entail additional costs, which will be discussed further.

Acute IS care

Thrombectomy and thrombolysis are two important components of acute care in the IS context [13]. Mechanical thrombectomy costs range from an average of 6,518 USD in India [17] to 11,221 USD in China [18] and it is regarded as cost-effective at about 11,608 USD per acquired QALY [18]. However, considerable out-of-pocket costs, ranging from 2,109 USD to 5,274 USD, pose a significant affordability challenge [19]. Compared to thrombectomy, Thrombolysis is less expensive, ranging from 2,231 USD to 5,690 USD [20, 21]. Though, in a developing country like Iran, only 30% of patients may be able to afford thrombolysis without insurance [22]. The cost-effectiveness of the procedure ranges from 2,848 USD/QALY to 10,688 USD/QALY gained over a lifetime [20, 21]. Overall, thrombectomy and thrombolysis in an IS context in a developing country are found to be cost-effective, with expenditures ranging from 2,811 USD to 37,134 USD per gained QALY — [13]. However, without proper insurance, a significant number of people are unable to afford these procedures and must incur high out-of-pocket payments [17, 19].

Hospitalization and medication expenses are lower in IS compared to hemorrhagic stroke; nevertheless, due to the lack of specific data on IS costs, we have used mean expenses for all kinds. Of course, the mean expenses might be more representative of IS costs due to the higher frequency of IS. In developing countries, the cost of a stroke hospitalization varies depending on the type and severity of the stroke, the type of insurance, and the type of care center [23-26]. The cost of hospitalization varies from 592 USD per "year" in India to 624 USD per "day" in Lebanon [26, 27]. Even within the same country, costs vary; in China, for instance, expenditures range from 1,159 USD in total to 5,137 USD per stay [23, 25]. However, high self-payment ratios and insufficient reimbursement for both hospitalization and medications are commonly documented in studies of developing countries [23-26]. In a research done in China, out of total hospitalization charges of 1,792 USD, out-of-pocket payments were 505 USD, while insurance paid 71 percent of total costs [23]. Medication is also among the main sources of expenses, costing 1,309 USD in India to 1,614 USD in China. [9, 24, 25].

According to research by Heeley et al., approximately 20% of patients couldn't afford to purchase stroke medications on their own since they cost more than 30% of their annual income. Despite the fact that insurance covers a significant proportion of the costs, hospitalization and medications place a significant financial burden on stroke patients. So, many vulnerable groups, such as retirees and non-working populations, will be preserved if they have adequate insurance coverage [28].

Rehabilitation

The expenditure on IS rehabilitation varies depending on the country, initially received acute care, and the location of the rehabilitation. [20, 29]. In China, total rehabilitation costs range from $4,811 USD to $5,257 USD per year, depending on whether patients received thrombolysis [29]. This disparity is even more pronounced in Iran, where patients who receive initial thrombolysis treatments spend 3,215 USD annually while those who do not receive the procedure pay 7,080 USD per year [20]. This emphasizes the significance of acute medical procedures.

Furthermore, compared to the nursing home and home care, IS rehabilitation in special centers is substantially more expensive, 347 USD/day, 76 USD/day, and 567 USD/day, respectively [29]. All of them are regarded as cost-effective [30]. However, a rehabilitation center comes at a significant additional cost [29]. In developing countries, stroke rehabilitation is more complicated by a lack of insurance coverage or financial assistance, as well as high treatment prices [31].

Direct medical costs of IS in developed countries

Acute IS care

According to the latest available data, the United States has the lowest and highest lifetime thrombolysis expenses among developed countries, with 1,852 USD and 29,938 USD, respectively. In United States, lifetime cost-effectiveness of thrombolysis ranges from 7,719 USD/QALY to being referred to as “dominant” (over non-thrombolysis group) [10]. Approximately 84% of patients receiving thrombolysis in the United States are insured [32].

Thrombectomy is more cost-effective than thrombolysis for stroke patients, with lifetime costs ranging from 3,352 USD/QALY in the Netherlands to 16,422 USD/QALY in the United States [12], with extra expenses of an average of 51,897 USD [33] and average 308,192 USD [34], respectively. In large populations, this disparity in economic advantages is more obvious. In a 1,000-person population, the net monetary advantage of 24 hours thrombectomy was roughly 2.5 times that of 24 hours thrombolysis – 117 million USD against 45 million USD on average [35].

In a comprehensive systematic study undertaken by Rajsic et al., expenditures for each patient each month following a stroke, including hospitalization, medications, and rehabilitation, were found to be between 884 USD in Australia and 5,705 USD in the United States. In this research, all countries except for the United States had higher gross domestic product per capita when compared to expenses. The gross domestic product per capita in some countries was 4 times greater than the costs [36] indicating affordability independent of insurance coverage. As a result, most patients in developed countries are able to pay for such treatments on their own, despite the fact that the United States, Europe Union, and other industrialized countries have high-quality health insurance systems [32, 37]. Just in the United States, private health insurance provides more than 90% of the costs and public health insurance is free [32]. Therefore, stroke patients are less likely to experience financial troubles.

Rehabilitation

In the last three decades, the cost-effectiveness of stroke rehabilitation in developed countries has been a major concern. Some previous research revealed no strong evidence of its cost-effectiveness [38]. However, in 2017, world health organization (WHO) issued a call to action, titled "Rehabilitation 2030", to address the substantial requirements throughout the world. Integrating stroke rehabilitation into future stroke management plans can serve as confirmation of its cost-effectiveness [39]. The most recent research in industrialized countries on the economic evaluation of stroke rehabilitation supports the previously stated conclusion. For instance, in Taiwan, for every QALY gained, 165 USD and 45 USD are spent on hospital and home-based rehabilitation, respectively [40]. Furthermore, home-based rehabilitation is at least as successful as outpatient rehabilitation for sufferers [41].

41 After introduction of advanced therapeutic…

As previously stated, developed countries have a high-quality insurance system that covers patients. For instance, in the United States, more than % of stroke patients receive rehabilitation and are covered by insurance, which supports more than 90 percent of the costs [32].

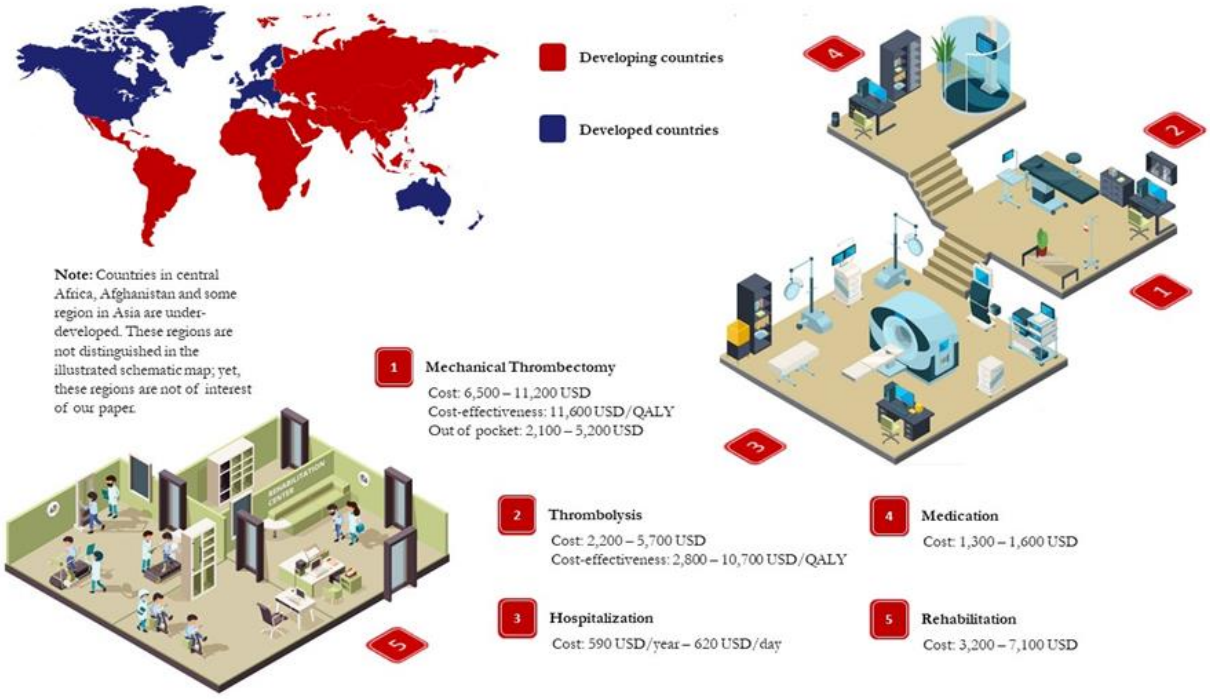

Figure 1. Direct medical costs, out of pocket expenses, insurance coverage, and cost-effectiveness of stroke treatments in developing countries.

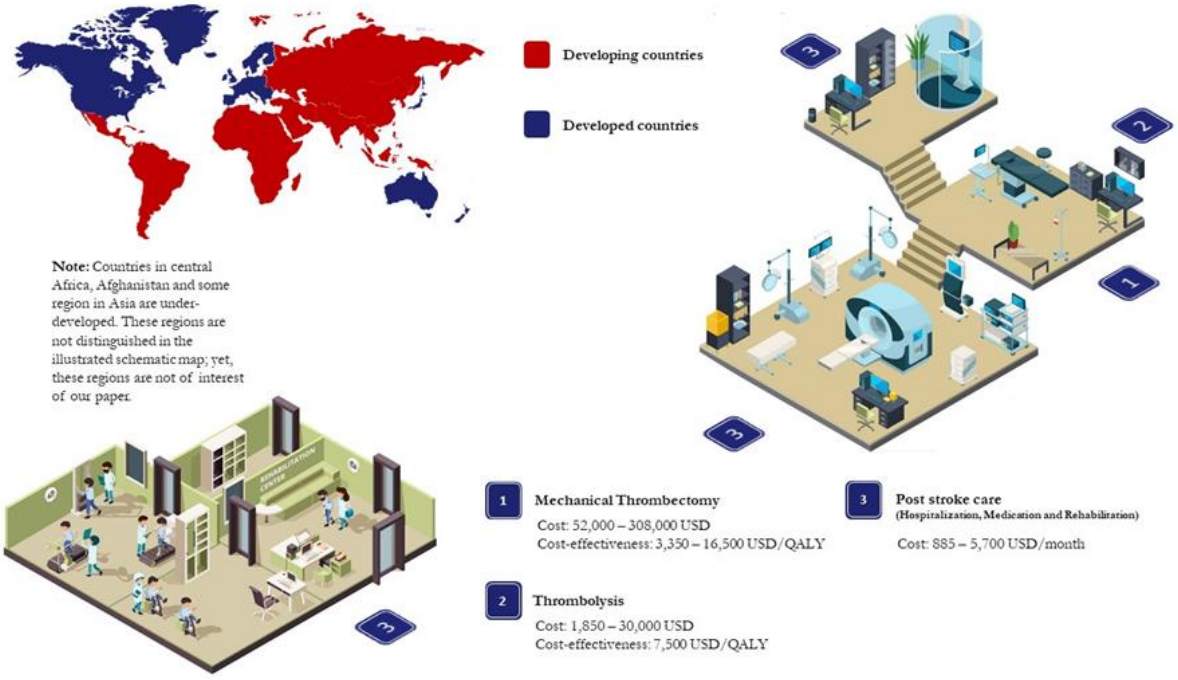

Figure 2. Direct medical costs, out of pocket expenses, insurance coverage, and cost-effectiveness of stroke treatment in developed countries

Direct medical costs ATMPs in ischemic stroke treatment

Despite the importance of conventional treatments, the adverse effects of these therapies should not be overlooked. For instance, thrombolysis has a limited therapeutic time window and can lead to neuroinflammation, ROS production, and intracranial hemorrhage [42, 43]. Also, the thrombectomy procedure does have a time limit of up to 24 hours. As well, to be a candidate for this procedure, the patient must meet specific criteria [44]. The thrombectomy technique can also only be performed in hospitals with advanced imaging technologies and skilled clinicians. Additionally, the thrombectomy procedure carries the risks of vascular injury, emboli, vasospasms, symptomatic hemorrhage, and other complications [45]. Therefore, there is an ongoing need for alternative treatment options due to the short therapeutic window and restricted applicability of both thrombolysis and thrombectomy. ATMPs are now being considered a novel therapeutic therapy for a variety of neurological diseases, including stroke. Stem-cell therapy and gene therapy are the main employed ATMPs fields in stroke treatment.

Cell-based therapy

Different therapeutic approaches have been qualified to join the clinical trial stage since the emergence of stem-cell therapy.

In the acute (within a week from stroke onset) and subacute (between 1 week to 6 months from onset) phases of the stroke, bone marrow mononuclear cells (BMMNCs) were the most commonly employed stem cells [46]. Stem cells, such as bone marrow mesenchymal stem (BMSCs) and induced pluripotent stem cells (iPSCs), must be cultured before being transplanted, while BMMNCs could well be obtained autologously immediately before administration, which could be critical in acute clinical care settings when compared to other cell sources [47]. In the acute phase, eight trials applied BMMNCs and the results were as follows:

- "Good" recovery (N=1)
- "Better" recovery compared to control (N=3)
- "Better" national institute of health stroke scale recovery (N=1)

In the sub-acute phase, out of seven studies that utilized BMMNCs, one study reported "good" recovery in the treatment group. According to the chronic phase of ischemic stroke (after 6 months from stroke onset), there are currently no effective treatments, hence the development of an effective treatment approach is eagerly awaited. Among all clinical trials using stem cells for this phase of IS, different types of stem cells were implemented but BMMNCs, mesenchymal stem cells (MSCs), and hematopoietic stem cells (CD34 Positive) were the cell types with "significant" recovery [48] Clinical trials reported above illustrate a trend of shifting from autologous to allogeneic cells, with the goal of large-scale commercial manufacture. However, several criteria, such as safety, effectiveness, affordability, and the possibility of manufacturing on a large scale, must also be considered before distributing a cell source for commercial applications [48]. There seems to be little information on the exact expenses of stem cell therapy for stroke, although it is estimated that this intervention would cost between 11,000 USD and 15,000 USD [49]. This implies that the cost of stem-cell therapy is comparable to that of thrombolysis or thrombectomy (as previously indicated), demonstrating its potential cost-effectiveness. The model given by Svensson et al. confirms this claim [50].

Gene therapy

As gene delivery strategies into the ischemic brain, viral vectors and non-viral polymer systems have been studied [51]. Adeno-associated viruses (AAVs) and lentiviruses (LVs) are now recommended in preclinical research of brain diseases due to their properties [52, 53], The use of NeuroD1 adeno-associated virus, which has been shown to have a considerable influence on regeneration in monkeys, is one of the most promising methods reported in animal research [54]. Until now, no gene therapy method for stroke treatment has been approved for clinical trials. As a result, it's ambiguous whether it's cost-effective or not. Despite this, the average cost of gene therapy is 768,925* USD, with the highest and lowest expenses being 2,383,472 USD to 77,401 USD, respectively. The cost-effectiveness of gene therapy ranges from 16,903 USD/QALY to 5.4 million USD/QALY, mostly depending on the type of disease – regardless of time [55].

∗ The given value was calculated by dividing "total delivery cost (per patient)" by the number of gene therapies with available "total delivery cost (per patient)." / Note: If the "total delivery cost (per patient)" cited had a range based on its "ancillary costs," we would compute the average and then add the value to other "total delivery cost (per patient)" s.

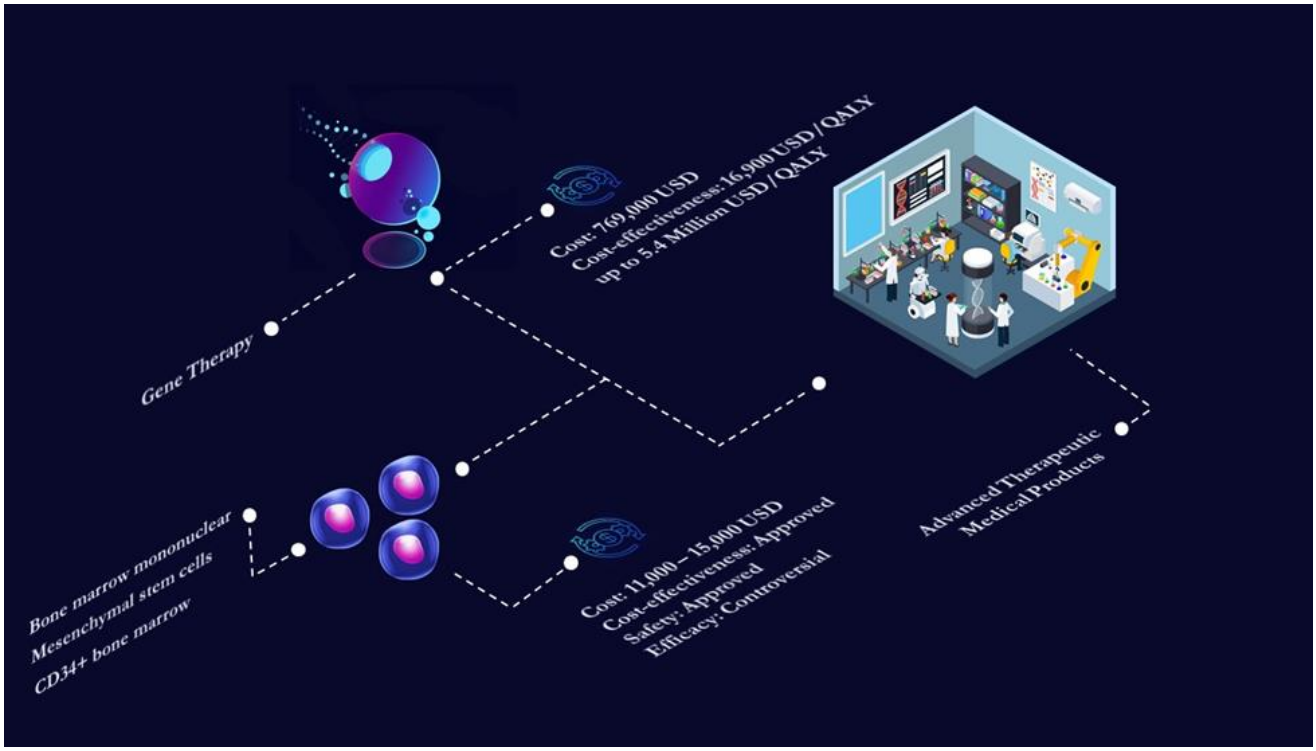

Figure 3. Advanced therapeutic medicinal products: costs and cost-effectiveness

Health insurance coverage of ATMPs: affordability challenge and solutions

ATMPs are considered to be cost-effective for the treatment of numerous diseases/conditions in many industrialized countries, however, there is no evidence in developing countries [15]. Nevertheless, the issue of ATMPs is not limited to cost-effectiveness. In this section, we focus on the case of the United States and the financial issues that gene therapy raises in the health insurance system.

Affordability

The most recent statistics available on total stroke spending in the United States show a total of $56.6 billion USD [4]. Approximately 795000 individuals have strokes each year, with IS accounting for nearly 87 percent of all attacks [56]. Considering that just 10% of all new IS patients are prospective candidates for gene therapy, the total cost will be close to 53 billion USD. This indicates that 10% of the IS population consumes 90% of the overall stroke-related budget. Certainly, many aspects are overlooked in the above example, but it presents a "big picture".

All in all gene therapy might even save money over the long term by lowering or eliminating current expenditures such as rehabilitation, hospitalization, and medications; yet, the economic burden of this intervention on both the insurance system and patients would be considerable [57]. This is not a challenge faced by stem-cell therapy since its prices are approximately equivalent to conventional procedures for stroke patients.

Solutions

There are a few approaches to address the challenges of affordability, each with its own set of pros and downsides; there are some techniques to addressing the difficulties of affordability, each with its own set of benefits and drawbacks; most of them benefit clients, while others benefit insurance providers. The general feature of client-supporting solutions is getting a loan from a third party (government and banks) to pay for treatment, then repaying the loan in installments over time. Producers could also offer installment payment plans as an alternative. Ultimately, if the death occurs or the therapy fails, the repayment procedure comes to an end [57]. To benefit insurance companies, the option of "reinsurance" should be available. Reinsurance means to provide insurers with insurance to buffer them from extreme pay-outs. This can save companies from exorbitant expenditures for each patient [57].

Conclusion

The most appropriate future implication for developing countries in the management of ischemic stroke is to focus on insurance coverage of acute IS care, as the outcome of ATMPs is dependent on patients' latest functional status, which has also proven to be extremely dependent on initial acute management. More emphasis should be placed on thrombectomy and at-home rehabilitation. Patients benefit even more from thrombectomy with greater expenses. Furthermore, while home-based and out-patient rehabilitation provides the same outcomes, home-based rehabilitation is more appropriate for stroke patients in underdeveloped countries due to budgetary constraints. On the other hand, a considerable proportion of the population in developed countries is financially capable of providing acute management services on their own. This, together with a qualified insurance system, guarantees that such therapies are affordable. Based on limited evidence on stem-cell therapy, the cost of stem-cell therapy is almost the same as that of thrombectomy and thrombolysis. Given the relative success, stem-cell therapy seems to have a bright future in both developing and developed countries. However, developing countries may encounter certain economic challenges. On the other hand, gene therapies for stroke treatment are mostly in the preclinical stage. Even if advances in the coming years result in a safe, efficient, and even cost-effective technology, the expenses of gene therapy continue to place an enormous strain on insurance systems in both developing and developed countries. To address this, government or bank loans, as well as installment payment plans, should be made available to patients.

Declaration

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Conflicts of interest/Competing interests

The authors declare no conflict of interest.

Authors' contributions

S.G drafted manuscript. M.A.M, S.K, S.S.N.P, and S.M.N edited and reviewed manuscript. M.V reviewed and approved the manuscript.

Ethics approval

Not applicable.

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