Original Article

Evaluation of COVID-19 Treatments in Iran in Comparison with Local Therapeutic Recommendations: A Population-Level Study on Utilization and Costs of Prescription Drugs

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ABSTRACT

Objective: In this study, we assess population-level data of COVID-19 treatments in Iran compared to Ministry of Health (MOH)-published guidelines to gain a better insight into the quality of care for this disease. **Methods:** National sales data of each recommended and nonrecommended COVID-19 medicine were used to proxy utilization between March 21, 2020, and March 21, 2021, or Iranian year 1399. COVID-19–attributed sales volume and number of patients were estimated by adjusting sales data with pre-COVID-19 average growth rate, recommended dose, and duration of treatment. Next, they were compared with the MOH guidelines in outpatient and inpatient settings. Furthermore, the list of top 10 molecules of the market and top 10 COVID-19–indicated molecules in terms of values were extracted to assess the economic burden of COVID-19 prescription drugs and their share. **Findings:** The estimated number of patients receiving COVID-19 treatments in some outpatient medicines such as recommended hydroxychloroquine was over 2.2 million. Favipiravir and remdesivir were collectively about two inpatient medicines 260,000; however, neither of these two medicines was recommended in the MOH guidelines. In some fewer specific medicines such as dexamethasone, prednisolone, azithromycin, and naproxen, the estimated number of COVID-19–attributed patients were incomparable with the officially announced number of confirmed cases in the year of study, which could be related to nonconfirmed diagnosed cases, irrational use, or prescribing, or limitations of our data and study. The total COVID-19–attributed market of candidate medicines was over 15 trillion IR Rials (almost 4.3% of the total market). Remdesivir, with over 60% of the total COVID-19 attributed market, followed by favipiravir, was among the highest value medicines. **Conclusion:** Despite the release of the COVID-19 guideline by Iran MOH, misalignment in the enforcement of decisions was a serious weakness (cases of favipiravir and remdesivir). This weakness led to some economic burden on the health-care system and raised ethical concerns.

Keywords: *COVID-19, guideline, medicine, utilization*

Introduction

Assessment of health policies and their impacts could provide policymakers of different countries with valuable information about the outcome of decisions for similar challenges and help them make better decisions

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in the future.[1-4] COVID-19, under the name of a novel coronavirus, was first announced to be observed in a cluster of cases in Wuhan, China, on December 31, 2019, and rapidly spread over different parts of the world like a pandemic. Since the pandemic, the WHO reported almost 240 million confirmed cases and nearly 5 million death tolls globally.[5] In Iran, the first documented case of COVID-19 was registered on February 19, 2020, and since then, over 5.5 million confirmed cases have been reported by Iran Ministry of Health (MOH), of which 121,000 of them died (until October 2021).[6]

From the 1st days to months of the pandemic, a few candidate medicines were introduced and used by clinicians as only potential treatments for COVID-19. Some clinical studies were conducted locally and internationally on their efficacy. Each of these potential medicines from different pharmacological groups was claimed to be effective for the management of COVID-19 infection.[7-10] Iran MOH COVID-19 scientific committee published the first version of the guideline for treating COVID-19 in February 2020, a few days after the first case in Iran was diagnosed.[11] This guideline was regularly revised afterward, considering the development of scientific evidence. Since the healthcare providers did not have any experience with COVID-19, they were supposed to rely on MOH recommendations fully. Thus, the case of COVID-19 could probably indicate the level of guideline-driven and evidence-based treatment in Iran. In this study, we will assess population level data of COVID-19 treatments in Iran in comparison with MOH-published guidelines to gain a better insight into the quality of care for COVID-19.

Methods

To evaluate this, we assessed the market of all potential COVID-19 medicines (either labeled or off-labeled) in Iran as a real-world population-level data source for Iran in the 1st year of being faced with the COVID-19 pandemic in Iran. First, we reviewed all versions of MOH therapeutic guidelines on COVID-19 management between March 21, 2020, and March 21, 2021. All medicines listed in at least one version were extracted with their recommended dose, treatment duration, and the eligible subgroup of patients. Next, we made a similarly comprehensive list of those nonrecommended medicines widely used in Iran to treat this disease.

Due to lack of access to reliable utilization data sources such as insurance claim databases, annual sales data of distributors to pharmacies were used as a proxy for utilization. Sales volume and value data for each medicine were extracted from the latest pharmaceutical sales data report (Amarnameh) published by Iran Food and Drug Administration (IFDA). This database provides pooled sales records of distributors to pharmacies collected, cleaned, and published by IFDA and is the most reliable source of pharmaceutical market data in Iran. The required data were extracted for the following time periods:

1) March 21, 2020, to March 21, 2021, or Iranian year 1399 (for the sake of simplicity, we name it as 2020 in this article)
2) March 21, 2019, to March 21, 2020, or Iranian year 1398 (for the sake of simplicity, we name it as 2019 in this article)
3) Four-year compound annual growth rate (CAGR) for the time before March 21, 2019 (almost before COVID-19 in Iran).

For medicines with some other approved indications and history of sales in the Iran market, the below formula was used to estimate COVID-19 attributed sales volumes:

COVID-19 attributed sales volume = (sales volume of 2020) − [2019 sales volume × (1 + CAGR4 year)].

Using this formula, the sales volume of 2019 and 4-year CAGR was used to estimate potential sales of each product in 2020 in the lack of COVID-19 situation, and then, the COVID-19–attributed sales volume could be estimated accordingly by deducting this number from the actual 2020 sale volume. For cases where the medicine was only applied to treat COVID-19 patients, 2020 sales volume data were considered without adjustment. Subsequently, recommended dose and average duration of treatment (DOT) for COVID-19 indication were used to estimate the number of patients. These medicines' individual and total budget impact was also calculated based on official sales data published by the IFDA. Furthermore, the list of top 10 molecules of the market and top 10 COVID-19–indicated molecules in terms of value were extracted to assess the economic burden of COVID-19 prescription drugs and their share.

Results

The MOH therapeutic guideline of COVID-19 covered treatment recommendations for outpatient and inpatient cases. In the latest versions, inpatient cases were also categorized into three sub-groups based on the severity of the disease. In Table 1, all recommended products are included in at least one version of these guidelines with their recommended dose and their recommendation status in the latest version.

Many recommended inpatient treatments were removed from guidelines in the newer versions later. Lopinavir/ritonavir, ribavirin, and oseltamivir were recommended

in the first version of the therapeutic guideline and widely demanded in the 1st months. Still, in the subsequent versions till the end of the time of this study, only lopinavir/ritonavir, atazanavir/ritonavir, and atazanavir remained with inpatients indication in medium-severity respiratory involvement, but later, they were also removed.

In addition to the above-mentioned list of medicines, a few more options were used during the pandemic in Iran, mainly in outpatient settings but not reflected or recommended in any MOH therapeutic guidelines. The list of these products is provided in Table 2.

In Table 3, each candidate product's sales data are provided for the last two Iranian years in terms of volume, then the growth rate of 2020 versus 2019 and 4-year CAGR.

As summarized in Table 3, for some products that are not exclusively indicated for COVID-19, volume growth in the 1st year of the pandemic is not comparable with their growth in the pre-COVID-19 period.

Figure 1a shows the top 10 ranking of pharmaceutical molecules in Iran in 2020. In its year of launch, remdesivir, with 1.5 million units' sales, gained over 2.7% share from the total pharmaceutical market in Iran as the number 1 molecule.

The total COVID-19–attributed market of candidate medicines was over 15 trillion IR Rials (almost 4.3% of the total market). Remdesivir with over 60% of the total COVID-19 attributed market followed by favipiravir and naproxen (each 7%) were the leading medicines in terms of value in the management of this disease in Iran. More details are provided in Figure 1b.

The market value ranking of COVID-19 medicines is not only driven by utilization, but also it could be related to the pricing mechanism and structure of different products. For instance, remdesivir, favipiravir,

Table 1: List of recommended medicines in the Ministry of Health guideline of COVID-19 management in Iran

Setting	Drug name	Dose
Outpatient	Oseltamivir 75 mg capsule	75 mg BID; 5 days
	Hydroxychloroquine 200 mg tablet	400 mg BID on the first day, then 200 mg BID; 5-10 days
	Chloroquine 150 mg tablet	300 mg BID on the first day, then 150 mg BID; 5-10 days
Inpatient	Oseltamivir 75 mg capsule	150 mg once daily; 5-14 days
	Hydroxychloroquine 200 mg tablet	400 mg BID on first day, then 200 mg BID; 7-10 days
	Chloroquine 150 mg tablet	300 mg BID on first day, then 150 mg BID; 7-10 days
	Lopinavir/ritonavir 200 mg/50 mg tablet	2 tablets BID; 7-14 days
	Ribavirin 200 mg capsule	600 mg BID; 5 days
	Atazanavir/ritonavir 300 mg/100 mg tablet	1 tablet once daily; 7-14 days
	Atazanavir 200 mg tablet	400 mg once daily; 7-14 days
	Interferon beta-1b 250 mcg injection	Every other day; 5-7 days
	Interferon beta-1a 44 mcg injection	Every other day; 5-7 days
	Dexamethasone 8 mg injection	8 mg once daily; up to 10 days
	Prednisolone 5 mg or 50 mg tablet	0.5 mg/kg; up to 10 days
	Tocilizumab 400 mg injection	8 mg/kg (assumption: one vial per patient)
	Remdesivir 100 mg injection	200 mg loading dose, followed by 100 mg daily (10 days)
	Heparin 5000 IU injection	5000 IU or 7500 IU TDS
	Enoxaparin 40 mg injection	Once daily

TDS: Three times a day, BID: Twice daily

Table 2: List of commonly used nonrecommended or disapproved medicines by Ministry of Health for COVID-19 management in Iran

Drug name	Common dose	Recommendation status
Favipiravir	1600 mg BID on first day, 600 mg BID following days; 7 days	Not recommended/included in insurance coverage list
Doxycycline	100 mg twice daily; 7 days	Not recommended anywhere
Azithromycin	500 mg once daily; 3 days	Not recommended anywhere
Ivermectin	12 mg twice daily	Not recommended anywhere
Colchicine	1 mg loading dose, followed by 0.5 mg 12 h later, then 0.5 mg BID; 7 days	Not recommended anywhere
Naproxen	250 mg TDS; 5 days (500 mg BID or TDS)	Only recommended for pain management

TDS: Three times a day, BID: Twice daily

Table 3: The market trend of candidate treatments of COVID-19 in Iran

Drug name	Sales volume 2019	Sales volume 2020	4-Y CAGR before 2019 (%)	Volume growth rate 2019-2020 (%)	Number of COVID-19 attributed patients in 2020
Hydroxychloroquine	56,675,000	105,835,000	7	87	2,260,000
Chloroquine	459,000	1,071,000	−21	134	35,000
Oseltamivir	3,239,000	6,654,000	−15	105	195,000
Lopinavir/ritonavir	1,724,000 (for COVID-19)	12,000	NA	−99	300
Ribavirin	678,000	1,764,000	−23	160	41,000
Atazanavir/ritonavir	-	-	NA	NA	-
Atazanavir	-	-	NA	NA	-
Interferon	10,364,000	5,849,000	6	−44	NA
Dexamethasone	37,203,000	40,387,000	−20	9	1,062,000
Prednisolone	205,707,000	266,112,000	3	29	5,400,000
Tocilizumab	-	31,000	NA	NA	31,000
Remdesivir	-	1,492,000	NA	NA	136,000
Heparin	15,762,000	30,244,000	14	92	1,754,000
Enoxaparin 40	7,960,000	11,515,000	10	45	394,000
Favipiravir	-	7,468,000	NA	NA	124,000
Doxycycline	46,648,000	56,254,000	−1	21	503,000
Azithromycin	203,166,000	294,791,000	5	45	13,578,000
Naproxen	152,677,000	371,766,000	2	143	10,802,000
Ivermectin	33,000	785,000	NA	2248	15,000
Colchicine	14,365,000	27,014,000	5	88	597,000

The numbers are round to nearest 1000. 4-Y CAGR=4-year compound annual growth rate, NA=Not available

and tocilizumab have higher prices than conventional products such as hydroxychloroquine and doxycycline, so their value in the market stands in a higher position.

Discussion

To the best of our knowledge, this study was the first study in Iran on the evaluation of COVID-19 treatment compared with MOH guidelines using population-level data. According to THE MOH official data, 1,781,421 patients with confirmed diagnoses of COVID-19 were registered in 2020. This number is consistent with the findings of our study, in which the estimated number of patients on main outpatient and inpatient treatments were comparable with official statistics. For instance, the estimated number of COVID-19–attributed patients for hydroxychloroquine and chloroquine is nearly 2.3 million. The observed difference could be justified by nonconfirmed cases which are not reflected in MOH data. Provided the 15% share of hospitalized cases out of total diagnosed patients in Iran,[12] the estimated number of patients on remdesivir and favipiravir (equivalent to 260,000 patients) as two reimbursed inpatient treatments consistent with THE official MOH data of confirmed cases.

However, there is a considerable inconsistency if we consider other inpatient recommended medicines such as dexamethasone (equivalent to about 1 million patients) and prednisolone (equal to about 5.4 million patients). Moreover, in cases of azithromycin and naproxen, 10 and 13 million patients were attributed to COVID-19 indication. This significant difference

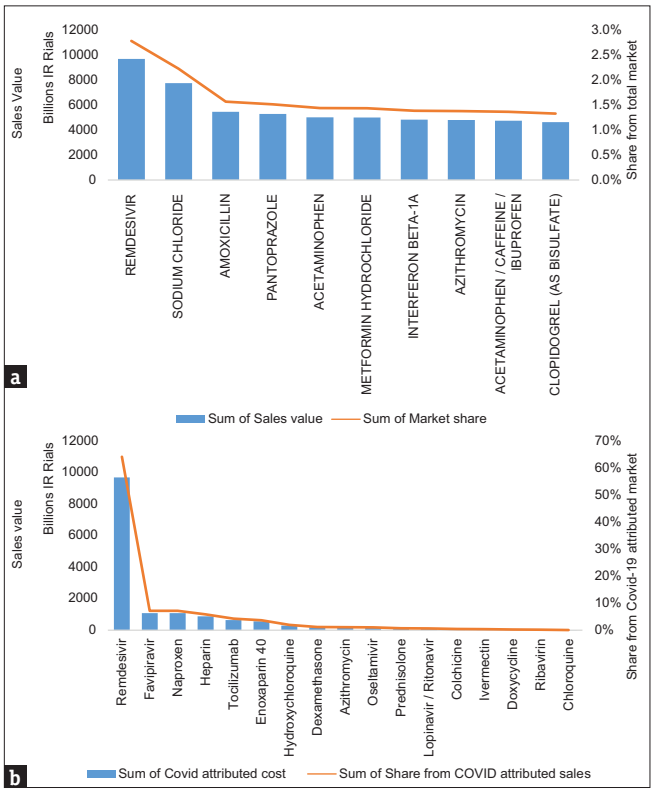

Figure 1: (a). Ranking of top 10 pharmaceutical molecules in Iran in 2020 (value and share from total market). (b) Sales value of COVID-19 candidate medicines and their share from COVID-19 attributed market in Iran 2020

between the estimated number of patients based on market data and official diagnosis rate could be related to our data source, which was sales record, not utilization. Thus, these excessive volumes could result from oversupply by companies and stock building at pharmacies or households. Irrational use regardless of recommended dose, indication and DOT could be another reason, especially in situation that these products were widely available in community pharmacies and their prices were very affordable, so they could have been easily prescribed by GPs and specialists in private sector.

This study also estimated the economic burden of COVID-19 medicines as one of these treatments became the highest ranked product in terms of value in the Iran pharmaceutical market with over 60% of COVID-19 medicines' cost.

Patients' access to medicines has always been a critical concern of the Iranian MOH,[13-15] so the promotion of generics and support of local manufacturers have been among the main policies during the last decades. Consequently, these local companies supply nearly 98% of the total market (volume).[16-18]

New COVID-19–related medicines, including favipiravir and remdesivir, were produced from the 1st months by local companies. Except for some cases of shortage that led to temporary importation, all market demands were addressed by local manufacturers. In the case of tocilizumab, the local biosimilar was also launched in the market for COVID-19. All other COVID-19 medicines were also being produced locally even before the pandemic.

In Iran, the role of the local pharmaceutical industry in the formulation and production of each candidate medicine in a short time was crucial inaccessibility of patients to these treatments. In the lack of such agile industrial infrastructure, access to treatments could have been very challenging for patients due to global shortage, the high price of imported brands, and limitations imposed by sanctions. On the other hand, since local companies provide a significantly higher level of accessibility and affordability to treatments, they might indirectly cause irrational use of such medicines in the pandemic in the lack of well-established monitoring mechanisms in insurance organizations on prescribing patterns.

It is pretty predictable that when such a new pandemic occurs and no proven treatment is available, society expects policymakers to take expedited pathways to approve potential treatments even before a complete package of evidence is formed.[19] In such cases, safety could be a high priority, efficacy might be assessed with more flexibility,[20] and cost-effectiveness as another part of the health technology assessment (HTA) process cannot be considered a very impactful variable. However, such emergency decisions should be revised regularly alongside the development of evidence. Governments could reassess each treatment based on a rolling-HTA dossier mechanism, in which all clinical, economic, social, and ethical are updated based on evolving evidence development. During the 1st year of the pandemic in Iran, a similar approach was taken by Iran MOH and IFDA. However, misalignment in the enforcement of decisions among different stakeholders was a serious weakness. For instance, remdesivir and favipiravir could be two examples of the most controversial antivirals cases in Iran claimed for COVID-19 management. Provided early results of some international studies on favipiravir and remdesivir[21-23] and clinicians' requests in the 1st months of the pandemic, IFDA finally accepted to include these two molecules in Iran's Drug List (IDL). However, in the case of favipiravir, the approved indication for IDL inclusion and marketing authorization was in influenza, not COVID-19. Favipiravir was not also recommended later in any MOH therapeutic guideline. However, it was added to the insurance coverage list for COVID-19 inpatient use.

Nevertheless, in the last version of the COVID-19 guideline in 2020, the MOH recommended against using all antiviral drugs, including remdesivir, favipiravir, lopinavir/ritonavir, atazanavir/ritonavir, and atazanavir, due to insufficient efficacy evidence. However, remdesivir and favipiravir were still in high demand and widely used by clinicians and hospitals. Tocilizumab was another controversial case. It was added to IDL for COVID-19 indication, while it was refused to be added to IDL a few years earlier for rheumatoid arthritis. Again, Tocilizumab was not recommended afterward in any therapeutic guideline of MOH till the end of the period of this study, except for clinical trials.

Evaluation of nonrecommended or disapproved treatment options showed that some of these medicines were widely used for COVID-19. For instance, sales of ivermectin, regardless of all disapprovals, has dramatically increased over 20 times which could be mainly related to claims of its effect on COVID-19.[24] Colchicine was apparently used to treat COVID-19 without any approval or recommendation, which led to an 88% increase in sales volume.

The main limitation of this study could be related to the weaknesses of ecological studies, which are more focused on total trends rather than individual-level

analysis. Access to individual-based databases, including health insurance and prescriptions, could provide a more profound insight into the level of evidence-based treatment and its variations over time, geographic regions, wealth-related inequalities, etc., The other limitation of this study was related to the source of data. In the lack of utilization data, we assumed that national-level sales of medicines are equivalent to utilization. This could be challenged because overproduction and oversees of a product could be considered as high utilization (probably the case of azithromycin). On the other hand, the shortage of a product like what was experienced for favipiravir and remdesivir could be misleading.

Although the evidence-based policymaking was followed from the 1st days by the Iran MOH, many misalignments existed among different sections to implement guidelines and recommendations. This weakness in crisis management led to some economic burden on the healthcare system and raised ethical concerns. More studies should be conducted to obtain a more comprehensive insight into the quality of policymaking and implementation in different parts of the health-care system during the pandemic.

Authors' Contribution

A. Hashemi-Meshkini and R. Koochak contributed in designing of study, S. Yaghoubifard, R. Koochak and A. Hashemi-Meshkini gathered data and wrote the manuscript, S. Nikfar, R. Koochak and E. Rezaei-Darzi were involved in analysis and interpretation, and finalizing the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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