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Variation in therapeutic strategies for the management of severe COVID-19 in India: A nationwide cross-sectional survey

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Abstract

Aim: During the pandemic of coronavirus disease 2019 (COVID-19), the physicians are using various off-label therapeutics to manage COVID-19. We undertook a cross-sectional survey to study the current variation in therapeutic strategies for managing severe COVID-19 in India.

Methods: From January 4 to January 18, 2021, an online cross-sectional survey was conducted among physicians involved in the management of severe COVID-19. The survey had three sections: 1. Antiviral agents, 2. Immunomodulators, and 3. Adjuvant therapies.

Results: 1055 respondents (from 24 states and five union territories), of which 64.2% were consultants, 54.3% working in private hospitals, and 39.1% were from critical care medicine completed the survey. Remdesivir (95.2%), antithrombotics (94.2%),

corticosteroids (90.3%), vitamins (89.7%) and empirical antibiotics (85.6%) were the commonly used therapeutics. Ivermectin (33%), convalescent plasma (28.6%) and favipiravir (17.6%) were other antiviral agents used. Methylprednisolone (50.2%) and dexamethasone (44.1%) were preferred corticosteroids and at a dose equivalent of 8 mg of dexamethasone phosphate (70.2%). There was significant variation among physicians from different medical specialities in the use of favipiravir, corticosteroids, empirical antibiotics and vitamins.

Conclusion: There is a considerable variation in the physicians' choice of therapeutic strategies for the management of severe COVID-19 in India, as compared with the available evidence.

1 | INTRODUCTION

The pandemic of coronavirus disease 2019 (COVID-19) had a significant impact on the healthcare systems globally and more so in third world countries, such as India.[1] India contributed to 19.2% of the global patient load of COVID-19 and second in position after the United States by the number of confirmed patients (as of 15 February 2021). However, the mortality is lower, with a patient fatality rate of 1.15% compared with 2.1% worldwide.[2] There has been some debate on the low patient fatality rate, and it depends on various factors including the average age of the population, patient reporting and testing strategies.[3-5]

More than 80% of the patients with COVID-19 have mild to moderate symptoms and may not require hospitalisation. However, 15%-20% of patients may develop severe COVID-19, which is defined as the presence of pneumonia and clinical signs of respiratory distress, or peripheral oxygen saturation (SpO_2) <90% on room air, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (Pao_2:Fio_2) of <300 mm Hg, or >50% lung infiltrates.[6] Patients usually develop severe COVID-19 one week after the onset of symptoms and can deteriorate rapidly, requiring hospital and intensive care unit (ICU) admissions.[7] The reported mortality in severe COVID-19 is 34%-50%, with a decline in the last few months.[8-10] The mortality in severe COVID-19 is dependent on various factors such as age, male sex, organ dysfunction, the severity of respiratory failure (lower PaO2/Fio2 ratio), and the requirement of invasive mechanical ventilation.[9-11]

The rapid growth of COVID-19 pandemic propelled off-label use of various drugs by physicians with little or no evidence. The Ministry of Health and Family Welfare (MOHFW), India, released the last guidelines on the clinical management of COVID-19 on 3 July 2020.[12] There has been significant research on the various treatment options for moderate-severe COVID-19 in the last few months. The landmark RECOVERY trial has revealed that dexamethasone can reduce significant mortality in patients on oxygen support or invasive mechanical ventilation while conferring no benefit in those not requiring oxygen.[13] In the absence of revision in the guidelines, there is an expected variation in the pharmacological management of COVID-19. We undertook a nationwide cross-sectional survey over two weeks in January 2021 to study the variation in the therapeutic strategies of severe COVID-19 in India.

What's known

- India contributed to 10.9% of the global patient load of COVID-19 and second in position after United States by the number of confirmed patients (as of 15 February 2021).
- The Ministry of Health and Family Welfare (MOHFW), India, released the last guidelines on the clinical management of COVID-19 on 3 July 2020.
- The rapid growth of COVID-19 pandemic propelled off-label use of various drugs by physicians with little or no evidence.

What's new

- The common therapeutic agents in the management of severe COVID-19 in India, include remdesivir, antithrombotics, corticosteroids, vitamins and empirical antibiotics.
- There is a significant variation among physicians of different medical specialities in the use of favipiravir, corticosteroids, empirical antibiotics and vitamins for severe COVID-19.
- There is a considerable variation in the physicians' choice of therapeutic strategies for severe COVID-19 in India as compared with the available evidence.

2 | MATERIALS AND METHODS

An online cross-sectional survey on the pharmacological treatment of severe COVID-19 using "Google forms" was conducted from 4 January to 18 January 2021. Eighteen physicians from

Critical Care Medicine, Anaesthesiology, Pulmonary Medicine and Internal Medicine involved in managing severe COVID-19 and representing prominent states were invited into the steering group. We searched "Google Scholar" and "PubMed" electronic databases using search terms "therapeutics," "pharmacological treatment," "management," AND "COVID-19," "SARS-CoV-2." We reviewed all English language, published research, including national guidance from MOHFW, India, World Health Organisation (WHO) on adult humans with COVID-19, published during 2020. With the help of a heterogenous steering group, we also included other off-label medications currently being used in India. The survey was then prepared using several qualitative or quantitative clinical practice points on the pharmacological treatment of severe COVID-19. A dry run of the survey was conducted among the steering group for any typographical mistakes and feedback. The survey was circulated to physicians through e-mail and social media channels and consent was taken from all respondents. A concerted effort was taken to invoke participation from all the states, public and private hospitals, and across all medical specialties involved in managing severe COVID-19.

The survey had 35 multiple-choice questions (including four on demographic details of the respondents). (Appendix 1: Copy of the original survey) The demographic data included the type and place of hospital of engagement, designation, and medical speciality for all respondents. The survey was divided into three sections: 1. Antiviral agents 2. Immunomodulators 3. Adjuvant therapies. The WHO criteria for the severity assessment of COVID-19 was used in this cross-sectional survey.[14] The respondents were allowed to select multiple options, based on either disease severity or clinical indications for the various therapeutic agents. The comments and feedback from participants were taken through the open comment section after questions. Duplication of entries was prevented through e-mail lock in the Google forms. The study was registered with Clinical trials.gov (Identifier: NCT04691921).

The descriptive analysis was used for absolute numbers and percentage (%). The pharmacological therapeutics were analysed based on the severity of illness, hospital type, working speciality and designation of the respondents in the hospital using the chi-square test. P-value less than 0.05 was taken as significant. IBM SPSS (version 26.0, Armonk, NY: IBM Corp.) was used for analysis.

3 | RESULTS

Over two weeks, 1063 complete responses were received, and1055 were finally analysed (responses from outside of India were removed). The respondents from 24 (85.7%) Indian states and five (62.5%) union territories participated in the survey, representing approximately 99.3% of Indian population (Figure 1). 64.2% of the respondents were consultants or senior consultants, 54.3% working in private hospitals and 31.9% in medical college. The top three medical specialities were critical care medicine (39.1%), anaesthesia (26.4%) and pulmonary medicine (11%) (Appendix 2, Figure 1).

Remdesivir (95.2%) and corticosteroids (90.3%), each for 5-10 days, were the most common therapeutics chosen by respondents. (Figure 2) The majority of the responders were using empirical antibiotics (85.6%), vitamins (89.7%) and antithrombotics (94.2%) as adjuvant therapies in severe COVID-19. 71.6% used remdesivir for severe COVID-19, while 65.2% and 53.6% for moderate and critical COVID-19, respectively (Tables 1 and 2). The other primary antiviral agent being used included ivermectin (33%), convalescent plasma (28.6%) and favipiravir (17.6%). 31.5% and 47% of respondents respectively, used ivermectin and convalescent plasma irrespective of the disease severity, while 80% used favipiravir for moderate illness. Tocilizumab is the other immunomodulator used by 40% of respondents, and even considered for non-severe disease. Regarding corticosteroids, methylprednisolone (50.2%) and dexamethasone (44.1%) were the commonly prescribed agents with a preferred dose equivalent to 8 mg of dexamethasone phosphate (70.2%). (Table 2).

There was significant variation in the use of favipiravir ($P < .001$), and ulinastatin ($P = .034$) among respondents based on their designation in the hospital. (Figures 3 and 4) There was also a significant variation ($P = .005$) in the use of antiplatelets based on hospital type in severe COVID-19 (Figure 5). Antiviral agents {favipiravir ($P = .005$)}, corticosteroids ($P = .035$), and the use of adjuvant therapies {antibiotics ($P < .001$), and vitamins ($P < .001$)} were significantly variable, based on the working speciality of respondents (Figures 3-5).

4 | DISCUSSION

The arduous clinical work during pandemic and rapidly evolving evidence made it difficult for physicians to keep abreast of the latest research. The deluge of information through print or social media, the pre-peer review release of the research, and political interference in the science have further perplexed physicians. Researchers globally have made substantial progress in the last few months to understand the pathophysiology and explore various therapeutic options for severe COVID-19.[13-16] We undertook this survey in January 2021, after the first wave of the pandemic of COVID-19 started receding in India, to study the variation in therapeutic strategies. Remdesivir, corticosteroids and prophylactic antithrombotics were the most common therapeutic agents used by the physicians to manage severe COVID-19. There was considerable use of empirical antibiotics and vitamins by the physicians. There was also significant variation among physicians based on their working specialities in the use of therapeutics such as favipiravir, corticosteroids, empirical antibiotics, and vitamins to manage COVID-19.

4.1 | Antiviral agents

Most of the responding physicians used remdesivir (95.2%) as the preferred antiviral agent in severe COVID-19 for 5-10 days (56.6%). However, 53.6% agreed to use remdesivir in critical COVID-19 or

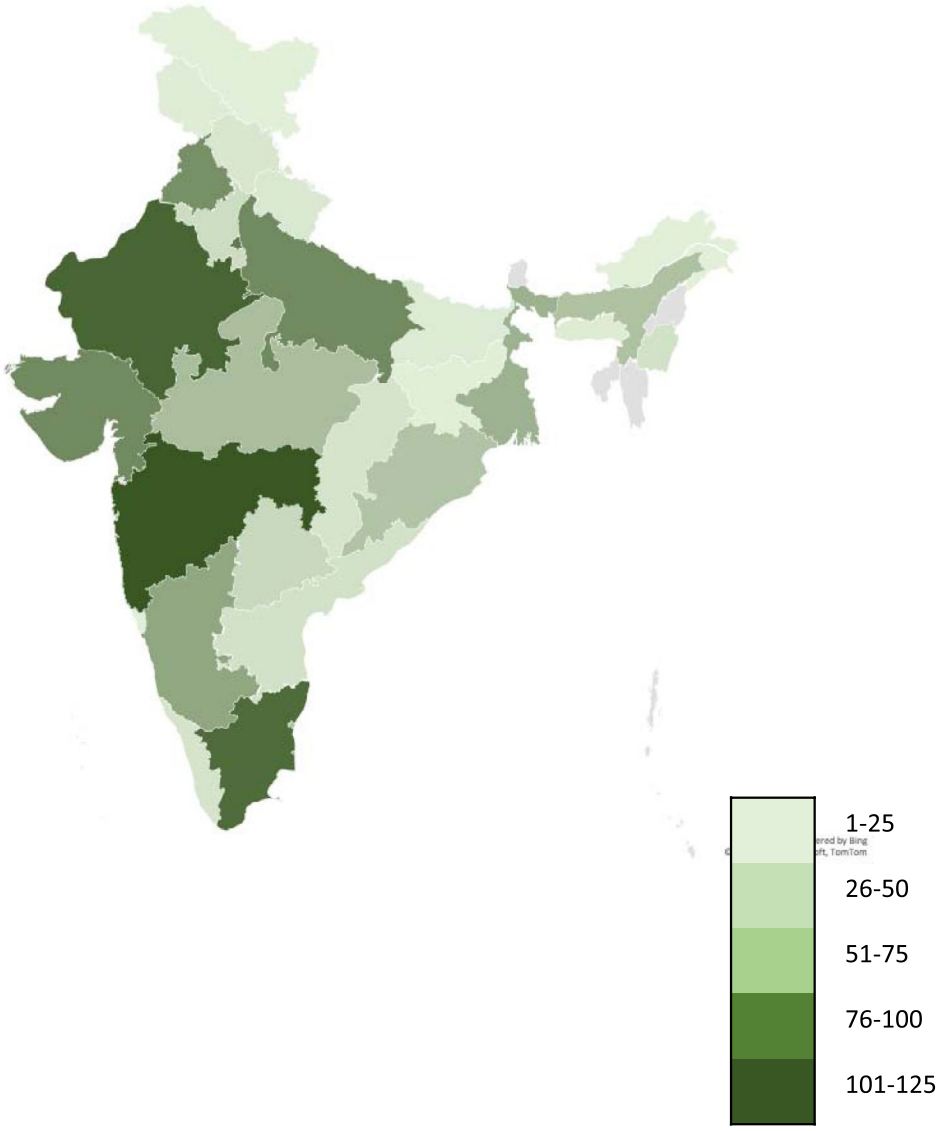


FIGURE 1 Geographical distribution of the survey respondents. Colour scale represents the number of participants from respective state or union territory

patients requiring invasive mechanical ventilation (50.2%). Recently, a meta-analysis of three randomised controlled trials (RCT) with 7600 patients concluded remdesivir did not reduce 28-day mortality in COVID-19.[17] However, on subgroups analysis, remdesivir showed to reduce mortality in patients requiring supplemental oxygen {relative risk (RR) 0.80} but not in mechanically ventilated patients (RR 1.16).[17]

Thirty-three per cent of the respondents used ivermectin in severe COVID-19 for 1-3 days (65.2%). However, 52% of respondents admitted using ivermectin in COVID-19 irrespective of the disease severity. The available evidence on ivermectin is based on small studies, non-severe disease, different doses or schedule or mostly non-peer-reviewed studies. National Institute of Health (NIH), after reviewing the available evidence, recently revised its recommendation on ivermectin from "against" to "insufficient evidence" for the use of ivermectin in COVID-19.[18] The ongoing trials of ivermectin in severe COVID-19 [NCT04646109, NCT04602507, NCT04746365] may provide some evidence in the future. Most of the respondents (82.4%) [senior consultants (90.7%) and consultants (87.6%)] were using favipiravir in moderate COVID-19. (Figure 3) However, a significantly higher number of postgraduate trainees (8.6%) and junior residents (5.4%) admitted using favipiravir in critical COVID-19. Similarly, there was a significantly higher use of favipiravir in critical COVID-19 among physicians from non-frontline medical specialities (9.0%). The use of favipiravir is discrepant with MOHFW guidelines on clinical management protocol for COVID-19 and available evidence.[12,19]

Two-third of the respondents who agreed to use convalescent plasma in severe COVID-19 used a single session or dose. The largest RCT on convalescent plasma from India in non-critical COVID-19

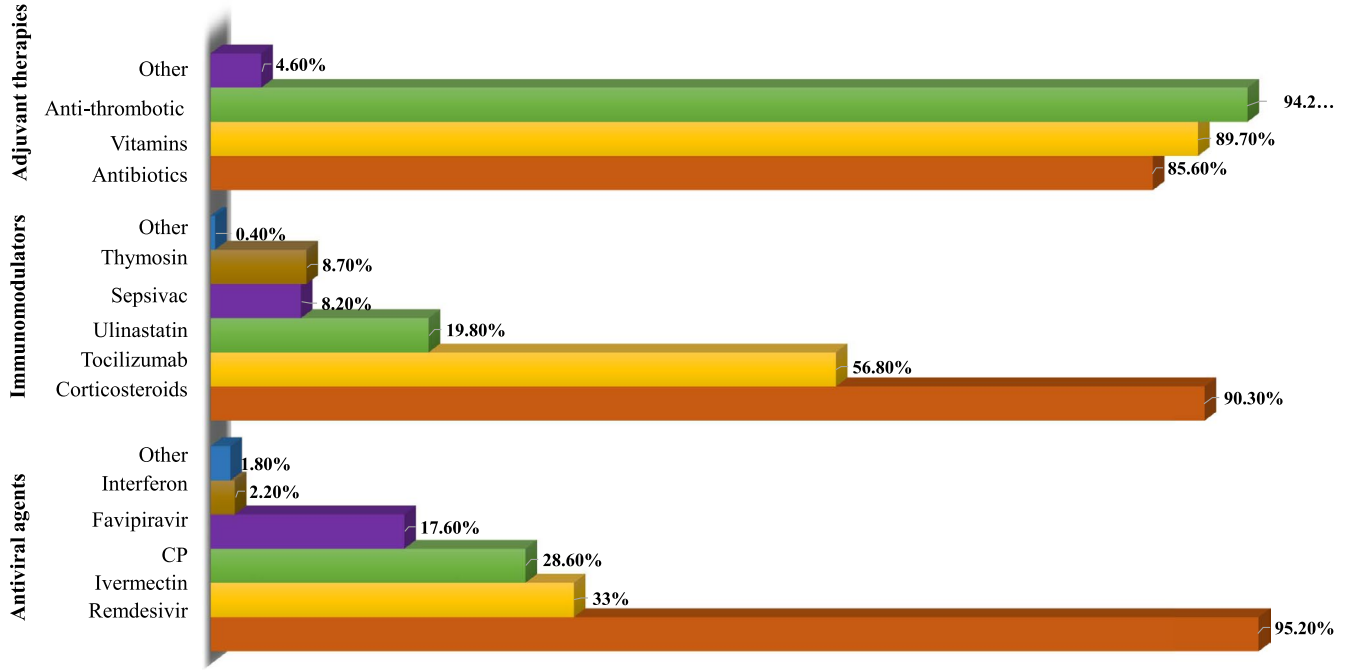


FIGURE 2 Percentage of respondents using various therapeutics to manage severe COVID-19. CP, convalescent plasma

TABLE 1 Percentage of use of different pharmacological agents based on the severity and respiratory support for COVID-19

Drugs	All patients irrespective of severity	Moderate COVID-19	Severe COVID-19	Critical COVID-19	Oxygen requirement for Spo2>90%	On IMV	Do not use
Antiviral agents							
Remdesivir	8.3%	65.2%	71.6%	53.6%	64.3%	50.2%	8.3%
Favipiravir	3.5%	30.4%	4.5%	2.3%	8.1%	1.8%	61.8%
Ivermectin	31.5%	26.4%	10.5%	7.3%	10.2%	6.1%	41.9%
Convalescent plasma	47.3%	20.9%	33.1%	27.9%	19.9%	17.7%	1.6%
Interferon	0.7%	2.2%	6.7%	7%	3.3%	4.5%	88.2%
Immunomodulators							
Corticosteroids	18.6%	57.1%	64.6%	55.3%	70.1%	51.1%	0.6%
Tocilizumab	40.4%	31.3%	31.1%	12.8%	38.1%	19.1%	34.2%
Itolizumab	9.3%	2.3%	8.3%	8.7%	12.2%	4.9%	82.5%
Ulinastatin	1.1%	8.9%	17.7%	16.3%	9.9%	11.1%	75.2%
Sepsivac	0.9%	3.6%	8.4%	8.3%	3.9%	4.9%	85.6%
Thymosin	0.7%	4.8%	8.6%	8.1%	5.1%	5.4%	87.4%
Adjuvant therapies							
On the basis of laboratory markers							
Empirical antibiotics	28.2%	33%	47.5%	46.1%	33%		7.5%
Thromboprophylaxis anticoagulants	28.9%	48.1%	58.3%	55.3%	56.4%		0.5%
Anti-platelets	13.3%	18.7%	29.2%	26.6%			51.9%
Multi-vitamins	69.7%	18.3%	21.1%	20.5%	8.2%		7.7%

Abbreviation: IMV, invasive mechanical ventilation.

TABLE 2 Percentage of responses on duration or dose of different pharmacological agents

Remdesivir	5-10 d depending on severity	5 d	10 d	>10 d	
	56.6%	40.6%	2.6%	0.2%	
Favipiravir	<7 d	7-14 d	>14 d		
	28.6%	69.6%	1.8%		
Ivermectin	1 dose	1-3 d	>3days		
	4.1%	65.2%	30.7%		
Interferon	<5 d	5-10 d	>10 d		
	58.6%	38.2%	3.3%		
Convalescent plasma	1 session	2 session	>2 session		
	66.3%	26.9%	6.9%		
Corticosteroids duration	<5 d	5-10 d	>10 d	>10 d based on laboratory markers[a]	
	9.6%	45.9%	13.3%	50.2%	
Corticosteroids type	Hydrocortisone	Dexamethasone	Methylprednisolone	Prednisolone	Any corticosteroid
	1.9%	44.1%	50.2%	1.5%	2.3%
Corticosteroids dose[b]	8 mg	9-16 mg	>16 mg		
	70.1%	20.6%	9.3%		
Tocilizumab	1 dose	2 doses	>2 doses		
	39.5%	57.2%	3.3%		
Itolizumab	1 dose	2 doses	>2 doses		
	47.2%	45.3%	7.5%		

[a]Extended duration based on the clinical response and inflammatory biomarkers.

[b]Corticosteroid dose in equivalent of dexamethasone phosphate.

failed to show any mortality benefit.[20] In a recent metanalysis of 10 published and pre-published RCT, the use of convalescent plasma in COVID-19 was not associated with a decrease in mortality or any other benefit.[21]

4.2 | Immunomodulators

The majority (90.3%) of the respondents agreed to the use of corticosteroids in severe COVID-19. There was, however, a divide, between methylprednisolone (50.2%) and dexamethasone (44.1%) as the preferred choice of corticosteroid. The equivalent dose and duration of corticosteroids also caused a split up among respondents; 29.9% opted for higher doses (>8 mg), and 50.2% for a longer duration (>10 days) based on the clinical response and inflammatory biomarkers. A significantly higher number of anaesthesiologists (12.5%, $P = .035$) admitted using corticosteroids in COVID-19, irrespective of the disease severity. The role of corticosteroids in reducing mortality in severe COVID-19 has already been proven.[13,22] However, controversy still exists on the choice, dose and duration of corticosteroids. The surviving sepsis guidelines on COVID-19 recommended dexamethasone over other corticosteroids at 6 mg/d dose for ten days to manage severe and critical COVID-19 based on a weak recommendation with shallow quality evidence.[23]

More than half of respondents (56.8%) admitted using tocilizumab in severe COVID-19 in two doses (57.2%) of maximum 8 mg/kg each. Thirty-one per cent respondents used tocilizumab in critical COVID-19 or patients requiring invasive mechanical ventilation (38%). The evidence for tocilizumab is conflicting so far, with various RCTs not finding any mortality benefit.[24] However, National Institute of Health and Care Excellence (NICE), revised its guidance based on the preliminary results of the REMAP-CAP study. It approved the use of tocilizumab in severe or critical COVID-19 and in those receiving respiratory or cardiovascular organ support in ICU.[25,26]

19.8% of the respondents, especially consultants, were using ulinastatin (a urinary trypsin inhibitor) in severe COVID-19. 8.2% of respondents also agreed to use sepsivac (heat-killed Mycobacterium W), and 8.7% thymosin (purified peptide from bovine thymic tissues) as immunomodulators for severe COVID-19. There are no prospective studies available on these therapeutics in COVID-19, and some of them are undergoing trials at present in India.[27]

4.3 | Adjuvant therapies

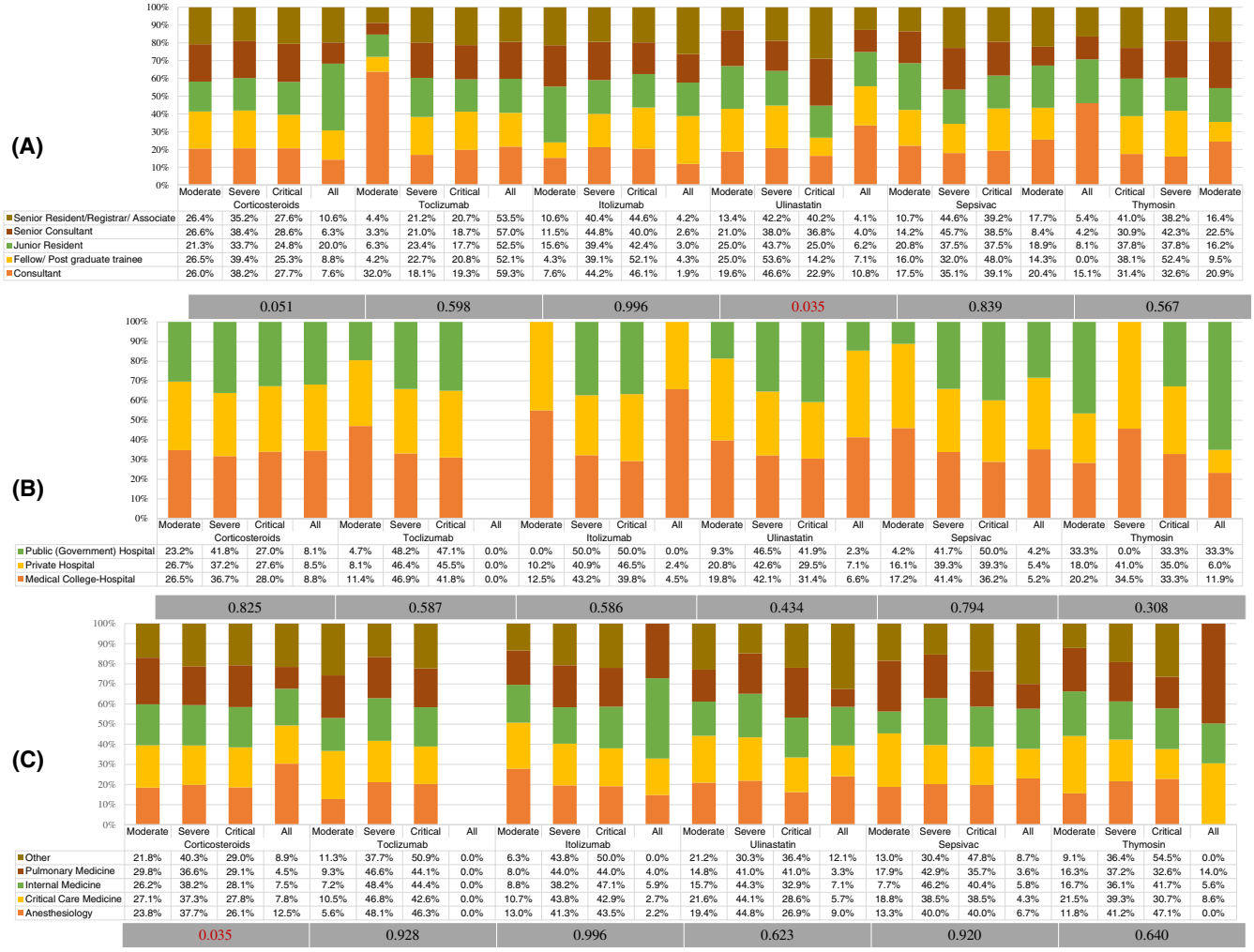
Considerable respondents (85.6% and 89.7%, respectively) admitted using empirical antibiotics and vitamins (vitamin C and vitamin D) in severe COVID-19. Azithromycin or doxycycline was commonly

FIGURE 3 Percentage distribution of the use of antiviral agents by participating physicians according to the severity level of COVID-19. A, Based on hospital designation of participants. B, Based on participants' hospital type. C, Based on speciality of participants. Grey bar represents the p-value using the chi-square test for variation

prescribed antibiotics with severity of COVID-19 (58.3%) or increased inflammatory markers (56.4%) were preferred indications. There was significant variation in the use of adjuvant therapies with specialists from critical care medicine preferred use of antibiotics in severe and critical COVID-19, while anaesthesiologists preferred vitamins in all patients of COVID-19.

Bacterial co-infections are uncommon in COVID-19 and vary from 3.5% at the time of admission to 15% among hospitalised patients.[28] A recent guideline on antimicrobials in COVID-19, recommended a restrictive approach and empirical antibiotics to be considered only if clinical, imaging and biochemical markers suggest a bacterial co-infection. The de-escalation of antibiotics within 48 hours is suggested if representative cultures or antigen tests excluded bacterial co-infection.[29] The authors did not recommend any empirical antibiotic regimen and advised to use community or hospital-acquired pneumonia guidelines while starting antibiotics and using local antimicrobial surveillance.[29] Recently, the RECOVERY trial found no role of azithromycin in the treatment of hospitalised COVID-19 patients.[30] The prepublication release from the PRINCIPAL trial using azithromycin or doxycycline for 14 days showed no significant benefit in time to recovery or hospitalisation.[31] NIH does not recommend vitamin C in COVID-19 because of insufficient data.[32] There are ongoing trials on intravenous vitamin C in COVID-19 (NCT04323514, NCT04401150, NCT04357782, NCT04264533, NCT02735707). The currently available evidence on vitamin D in COVID-19 is also controversial and cannot be used for its standard recommendation.[33] The high usage of prophylactic antithrombotic by respondents in this survey for severe COVID-19 is in line with recently published surviving sepsis campaign guidelines.[23]

Forty-eight per cent of the respondents admitted using prophylactic antiplatelets in severe or critical COVID-19 with the significantly



(A)

	Corticosteroids				Toclizumab				Itolizumab				Ulinastatin				Sepsivac				Thymosin			
	Moderate	Severe	Critical	All	Moderate	Severe	Critical	All	Moderate	Severe	Critical	All	Moderate	Severe	Critical	All	Moderate	Severe	Critical	Moderate	All	Critical	Severe	Moderate
Senior Resident/Registrar/ Associate	26.4%	35.2%	27.6%	10.6%	4.4%	21.2%	20.7%	53.5%	10.6%	40.4%	44.6%	4.2%	13.4%	42.2%	40.2%	4.1%	10.7%	44.6%	39.2%	17.7%	5.4%	41.0%	38.2%	16.4%
Senior Consultant	26.6%	38.4%	28.6%	6.3%	3.3%	21.0%	18.7%	57.0%	11.5%	44.8%	40.0%	2.6%	21.0%	38.0%	36.8%	4.0%	14.2%	45.7%	38.5%	8.4%	4.2%	30.9%	42.3%	22.5%
Junior Resident	21.3%	33.7%	24.8%	20.0%	6.3%	23.4%	17.7%	52.5%	15.6%	39.4%	42.4%	3.0%	25.0%	43.7%	25.0%	6.2%	20.8%	37.5%	37.5%	18.9%	8.1%	37.8%	37.8%	16.2%
Fellow/ Post graduate trainee	26.5%	39.4%	25.3%	8.8%	4.2%	22.7%	20.8%	52.1%	4.3%	39.1%	52.1%	4.3%	25.0%	53.6%	14.2%	7.1%	16.0%	32.0%	48.0%	14.3%	0.0%	38.1%	52.4%	9.5%
Consultant	26.0%	38.2%	27.7%	7.6%	32.0%	18.1%	19.3%	59.3%	7.6%	44.2%	46.1%	1.9%	19.6%	46.6%	22.9%	10.8%	17.5%	35.1%	39.1%	20.4%	15.1%	31.4%	32.6%	20.9%

(B)

	Corticosteroids				Toclizumab				Itolizumab				Ulinastatin				Sepsivac				Thymosin			
	Moderate	Severe	Critical	All	Moderate	Severe	Critical	All	Moderate	Severe	Critical	All	Moderate	Severe	Critical	All	Moderate	Severe	Critical	All	Moderate	Severe	Critical	All
Public (Government) Hospital	23.2%	41.8%	27.0%	8.1%	4.7%	48.2%	47.1%	0.0%	0.0%	50.0%	50.0%	0.0%	9.3%	46.5%	41.9%	2.3%	4.2%	41.7%	50.0%	4.2%	33.3%	0.0%	33.3%	33.3%
Private Hospital	26.7%	37.2%	27.6%	8.5%	8.1%	46.4%	45.5%	0.0%	10.2%	40.9%	46.5%	2.4%	20.8%	42.6%	29.5%	7.1%	16.1%	39.3%	39.3%	5.4%	18.0%	41.0%	35.0%	6.0%
Medical College-Hospital	26.5%	36.7%	28.0%	8.8%	11.4%	46.9%	41.8%	0.0%	12.5%	43.2%	39.8%	4.5%	19.8%	42.1%	31.4%	6.6%	17.2%	41.4%	36.2%	5.2%	20.2%	34.5%	33.3%	11.9%

(C)

	Corticosteroids				Toclizumab				Itolizumab				Ulinastatin				Sepsivac				Thymosin			
	Moderate	Severe	Critical	All	Moderate	Severe	Critical	All	Moderate	Severe	Critical	All	Moderate	Severe	Critical	All	Moderate	Severe	Critical	All	Moderate	Severe	Critical	All
Other	21.8%	40.3%	29.0%	8.9%	11.3%	37.7%	50.9%	0.0%	6.3%	43.8%	50.0%	0.0%	21.2%	30.3%	36.4%	12.1%	13.0%	30.4%	47.8%	8.7%	9.1%	36.4%	54.5%	0.0%
Pulmonary Medicine	29.8%	36.6%	29.1%	4.5%	9.3%	46.6%	44.1%	0.0%	8.0%	44.0%	44.0%	4.0%	14.8%	41.0%	41.0%	3.3%	17.9%	42.9%	35.7%	3.6%	16.3%	37.2%	32.6%	14.0%
Internal Medicine	26.2%	38.2%	28.1%	7.5%	7.2%	48.4%	44.4%	0.0%	8.8%	38.2%	47.1%	5.9%	15.7%	44.3%	32.9%	7.1%	7.7%	46.2%	40.4%	5.8%	16.7%	36.1%	41.7%	5.6%
Critical Care Medicine	27.1%	37.3%	27.8%	7.8%	10.5%	46.8%	42.6%	0.0%	10.7%	43.8%	42.9%	2.7%	21.6%	44.1%	28.6%	5.7%	18.8%	38.5%	38.5%	4.3%	21.5%	39.3%	30.7%	8.6%
Anesthesiology	23.8%	37.7%	26.1%	12.5%	5.6%	48.1%	46.3%	0.0%	13.0%	41.3%	43.5%	2.2%	19.4%	44.8%	26.9%	9.0%	13.3%	40.0%	40.0%	6.7%	11.8%	41.2%	47.1%	0.0%

FIGURE 4 Percentage distribution of the use of immunomodulators by participating physicians according to the severity level of COVID-19. A, Based on hospital designation of participants. B, Based on participants' hospital type. C, Based on speciality of participants. Grey bar represents the p-value using the chi-square test for variation

higher number of physicians from public or medical college-hospitals in severe COVID-19. In a retrospective study of 412 patients, aspirin use was associated with reduced use of invasive mechanical ventilation, ICU admission and hospital mortality.[34] However, this association has not been proved in any prospective study so far and cannot be recommended as a standard therapy. NIH recommends the continuation of antiplatelets in patients on chronic antiplatelet therapy before COVID-19.[35]

4.4 | Strength and limitations

The strength of this study is its widespread representation from most states and union territories, public or private hospitals, and physicians from different rank or medicine specialities. Secondly, the large number (over 1000) of participation in a short time frame of two weeks helped capture practice variation over a wide range of therapeutic strategies. Thirdly, the study was conducted just after the number of patients started receding after the first wave of pandemic, which may have helped capture practices afresh over the last few months. Finally, we tried to include all possible therapeutics being used in India to manage severe COVID-19.

There are few limitations in this study. The data on the age and gender of responders was not collected. However, the decision making of physicians is closely linked to their designation in the hospital rather than age. The inherent limitations of a cross-sectional survey, such as respondents recall bias, a measure of point prevalence and failure to follow the trend is also applicable to this survey. We provided open space for comments after

	Antibiotics				Antithrombotics				Antiplatelets				Vitamins			
	Moderate	Severe	Critical	All	Moderate	Severe	Critical	All	Moderate	Severe	Critical	All	Moderate	Severe	Critical	All
Senior Resident/Registrar/ Associate	21.7%	31.3%	24.9%	22.0%	25.3%	29.8%	29.5%	15.4%	19.1%	34.4%	30.1%	16.4%	12.1%	15.8%	16.2%	55.8%
Senior Consultant	20.5%	33.9%	29.1%	16.5%	25.7%	30.5%	28.4%	15.4%	25.2%	31.3%	27.2%	16.3%	15.8%	18.7%	17.4%	48.2%
Junior Resident	16.0%	34.0%	21.5%	28.5%	23.5%	27.3%	26.5%	22.7%	20.7%	35.6%	32.2%	11.5%	15.3%	12.6%	16.2%	55.9%
Fellow/ Post graduate trainee	20.0%	33.6%	27.9%	18.6%	22.9%	29.9%	30.6%	16.7%	15.5%	33.8%	36.6%	14.1%	12.1%	13.1%	14.0%	60.7%
Consultant	17.3%	33.8%	26.8%	22.1%	25.8%	31.8%	29.3%	13.1%	20.9%	33.3%	31.0%	14.7%	14.1%	16.3%	14.7%	54.9%

	Antibiotics				Antithrombotics				Antiplatelets				Vitamins			
	Moderate	Severe	Critical	All	Moderate	Severe	Critical	All	Moderate	Severe	Critical	All	Moderate	Severe	Critical	All
Public (Government) Hospital	18.4%	33.8%	25.2%	22.6%	24.3%	29.6%	28.8%	17.3%	20.7%	34.1%	29.6%	15.6%	9.8%	15.5%	18.4%	56.3%
Private Hospital	18.2%	33.6%	28.0%	20.2%	25.0%	30.3%	28.3%	16.4%	20.4%	30.6%	29.7%	19.3%	14.4%	16.2%	14.5%	54.9%
Medical College-Hospital	21.0%	32.8%	25.3%	20.9%	26.0%	31.6%	30.4%	12.0%	22.9%	37.1%	31.6%	8.4%	15.4%	16.9%	16.9%	50.8%

	Antibiotics				Antithrombotics				Antiplatelets				Vitamins			
	Moderate	Severe	Critical	All	Moderate	Severe	Critical	All	Moderate	Severe	Critical	All	Moderate	Severe	Critical	All
Other	18.2%	30.9%	20.0%	30.9%	26.3%	28.4%	29.5%	15.8%	21.9%	34.2%	30.1%	13.7%	15.6%	11.1%	11.1%	62.2%
Pulmonary Medicine	18.6%	34.8%	27.9%	18.6%	26.8%	31.9%	30.4%	10.9%	22.5%	32.6%	32.6%	12.4%	13.2%	18.5%	17.9%	50.3%
Internal Medicine	20.2%	33.8%	25.6%	20.5%	25.7%	32.4%	30.0%	12.0%	24.1%	33.7%	27.6%	14.6%	14.0%	16.2%	18.3%	51.5%
Critical Care Medicine	19.4%	34.6%	30.6%	15.5%	25.7%	30.4%	28.1%	15.8%	20.0%	32.4%	31.4%	16.2%	16.1%	19.1%	17.8%	47.0%
Anesthesiology	18.7%	31.1%	22.6%	27.6%	23.2%	29.4%	29.0%	18.3%	20.0%	34.0%	30.4%	15.6%	10.8%	12.0%	10.8%	66.4%
	0.000				0.503				0.995				0.002			

FIGURE 5 Percentage distribution of the use of adjuvant therapies by participating physicians according to the severity level of COVID-19. A, Based on hospital designation of participants. B, Based on participants' hospital type. C, Based on speciality of participants. Grey bar represents the p-value using the chi-square test for variation

few questions to collect practice variations throughout the pandemic. Finally, we did not include therapeutic anticoagulation in this survey.

5 | CONCLUSION

Remdesivir, corticosteroids, and prophylactic antithrombotics are the most used therapeutic strategies in managing severe COVID-19 in India. There is considerable use of empirical antibiotics and therapeutic vitamins by physicians in severe COVID-19. There is variation among physicians on the use of pharmaceutical agents in comparison to available evidence. Periodical update on the national guidelines is required to educate physicians on the rapidly evolving evidence.

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DISCLOSURE

All authors declare no conflict of interest related to this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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