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Evaluation of Ayurveda in the Management of Critically Ill COVID-19 Patients in an Intensive Care Unit: An Early Pandemic Retrospective Case-Control Study

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SUMMARY

While theorists and clinicians propose Ayurvedic medicines have a salutary therapeutic effect on infectious diseases by strengthening the body's natural immunity, few attempts have been made to examine this possible effect on the SARS-COV-2 virus during the early stages of the COVID-19 pandemic. This study seeks to redress this evidentiary shortfall in critically ill patients.

The primary objective of the study is an investigation of survival rates of critically ill COVID-19 patients who were admitted to an intensive care unit (ICU) of a hospital in India and administered Ayurvedic

medicines along with standard modern Western medical (MWM) treatment. In a case-control study design of 241 critically ill COVID-19 patients, we compared the clinical outcomes of two groups: one group of 110 patients who received government-mandated MWM treatment; and a voluntary group of 131 patients who received both MWM treatment and recommended Ayurvedic medicines according to a Government-approved protocol.

Using logistic regression analysis, findings indicate the odds of survival for ICU patients who received both MWM and Ayurvedic medicine were 2.5 times those who received MWM only, representing an increase of 154% in the odds of survival. This study of critically ill patients thereby provides preliminary evidence of the association of Ayurvedic therapeutics and COVID-19 patients in critical care during the early phase of the pandemic in India.

INTRODUCTION

Focus during the early stages of the COVID-19 pandemic was on preventive social measures to minimise interpersonal contact and on therapeutic strategies designed to attack the SARS-COV-2 virus and/or to immunise the population against it. However, according to India's Ministry of AYUSH, "Ayurveda…can certainly play a pivotal role to augment preventive measures….The current understanding of COVID-19 indicates that good immune status is vital to prevention and to safeguard from disease progression" [1]. Such a view was echoed by others [2,3], including Rajkumar who suggested Ayurveda "could be beneficial both in terms of psychological quality of life, and in terms of moderating the risk of [SARS-COV-2] infection" [4] and Tillu et al. who contended that "several general [Ayurvedic] measures…may be useful to reduce the risk of SARS-COV-2 infection and complement therapeutic management as an add-on treatment" [5].

However, Gautam et al. also pointed out at the time that "further pre-clinical and clinical trials need to be done for the evaluation of safety and efficacy of [the] polyherbal formulation[s]" proposed by Ayurveda [6]. The purpose of this present clinical study therefore was to report the outcome of integrating Ayurvedic medicine in the management of COVID-19 patients in an intensive care unit in India.

Early in the pandemic, the Ministry of AYUSH issued an advisory for improving immunity against COVID-19 infection by advocating certain prophylactic medicines used in Ayurveda [1]. Since functioning of the

immune system is considered critical to the progression of an infectious disease, interventions advocated by the Ministry of AYUSH for enhancing immunity had been suggested. Such a view has an ancient, time-tested precedent. For example, according to Tillu et al.,

> *Charaka Samhita*, the classic of Ayurveda, describes epidemic management and defines immunity as the ability to prevent disease and arrest its progress to maintain homeostasis. The concept of building strength of mind and body to cope with various stressors, including infection, is a cornerstone of Ayurveda practice. Similar to innate and acquired immunity, the Ayurveda concept of immunity (*Bala* or strength) is classified as natural (*Sahaja*), chronobiologic (*Kalaja*), and acquired (*Yuktikrut*) [5].

That is why Patwardhan and others argued that the immunomodulatory properties of Ayurvedic medicines like *Guduchi* (*Tinospora cordifolia*), *Shatavari* (*Asparagus racemosus*), and *Amalaki* (*Phylanthus emblica*) may have "the potential to bolster health and immunity of the community in the fight against SARS-COV-2 infection" [7]. Published preliminary clinical trials and case studies at the time, as summarised in Table 1, appeared to support these claims, although most of those publications related to experiences in mild cases.

In a randomised control study of 90 mildly-infected patients (organised into three groups of 30) who presented with fever and/or upper respiratory tract illness, Sanger et al. reported results related to the administration of: 1) modern Western medical (MWM) treatment as a control; 2) MWM treatment plus *Chyawanprash*, an Ayurvedic formula of 50 medicinal herbs and their extracts, including the prime ingredient of *Amla* (Indian gooseberry); and 3) MWM treatment plus a polyherbal Ayurvedic immune booster consisting of 11 ingredients, the principal ones being the 'King of Bitters' or Indian echinacea (*Andrographis paniculate*), turmeric (*Curcuma longa*), liquorice (*Glycyrrhizaglabra*), and *Tulsi* or holy basil (*Ocimum sanctum*) [8].

The study's dependent variables were serum counts for immunological cells CD3 (T-cells), CD4 (helper T-cells), and CD19 (natural killer T-cells), among other cells, and inflammatory markers like tumour necrosis factor (TNF-α) measured both before and 28-days after either 1), 2) or 3). Findings indicate that CD3, CD4, and CD19 serum levels increased significantly in the range of 30–80% and TNF-α levels decreased by 50%

in both groups 2) and 3), and patients in these Ayurvedic treatment groups recovered earlier than those in the control 1).

Table 1: Summary of Ayurvedic treatment results for COVID-19.

Study Type	Pathology and Symptomatology	Ayurvedic Treatment	Clinical Outcome	Citation
Randomised, controlled clinical trial of 90 patients who tested positive for COVID-19	Mild or very mild COVID-positive patients presenting with fever and/or upper respiratory tract illness	*Chyawanprash* formulated by processing 50 medicinal herbs, including the prime ingredient, *Amla* (Indian gooseberry) and a polyherbal immune booster	Increased CD3, CD4, and natural killer cells, and decreased elevated serum levels of tumour necrosis factor alpha (TNF-α)	[8]
Clinical case study of a high-risk 55-year-old male who tested positive for COVID-19	Comorbidities including diabetes mellitus, hypo-thyroidism, and chronic kidney disease, and symptoms including fever (pyrexia), sore throat, dry cough, body aches, weakness, loss of smell (anosmia) and taste (ageusia), and abdominal heaviness	Ayurvedic medicines (including *Guduchi*, *Ashwaganda Vati*, *Pathyadi Kwath*, and *Diabecon*), Yoga protocol, dietary recommendations, and lifestyle modifications, along with government-mandated compulsory modern Western medical (MWM) treatment	Clinical improvement in all symptoms within two days of starting treatment; 75% relief from symptoms after five days, and almost complete relief within nine days; normalisation of diabetes mellitus within 12 days	[9]
Clinical case study of a 26-year-old female who tested positive for COVID-19	Comorbidity of obesity, and symptoms including severe breathlessness, fever (pyrexia), sore throat, loss of smell (anosmia) and taste (ageusia), fatigue, chills, and headache (cephalgia); needed oxygen support during transport to hospital, with oxygen saturation at 80%	Ayurvedic medicines *Shadangapaniyam*, *Shaddharanacurna*, *Sukshmatriphala*, *Kanakasavam*, and *Indukantam Kashayam*, along with government-mandated compulsory modern Western medical (MWM) treatment	Clinical improvement within one day: able to eat, walk, and talk, and breathe without difficulty, with oxygen saturation stable at 95-98%; within next the two days, the patient was asymptomatic without oxygen support; and was discharged after a further seven days	[10]

Review of 100 longitudinal studies involving patients suffering from bronchial asthma (*Tamaka Shwasa*)	Patients with bronchial asthma presenting as either breathlessness (*Shwasakastata*), coughing (*Kasa*), rhinitis (*Pinasa*), throat irritation (*Kanthodhwamsa*), or sweating (*Lalatesweda*), who were tested before and after Ayurvedic treatment	Seven different Ayurvedic medicines called *Avalehas*, including *Vāsāvaleha*, were prepared according to ancient Ayurvedic texts and administered to patients for various lengths of time	Mostly significant statistical results showing reductions in bronchial asthma, such as $p < 0.001$ for six of the seven Ayurvedic medicines on breathlessness and coughing and $p < 0.01$ for *Vāsāvaleha* on throat irritation	[12]
Clinical trial of 23 patients with symptoms of bronchial asthma (*Tamaka Shwasa*)	Previous diagnosis of bronchial asthma, and current symptoms of breathlessness (*Shwasakastata*), coughing (*Kasa*), rhinitis (*Pinasa*), and chest pain (*Parshvashula*)	*Shunthyadi Churna*, which contains *Pippali* and *Marchia*, was administered three times a day after food for a period of six weeks	43% mild improvement, 38% moderate improvement, 19% marked improvement, and 0% complete remission of symptoms for bronchial asthma	[13]

In a single-patient clinical case study, Mishra et al. also reported improvement in all COVID-19 symptoms within two days of starting Ayurvedic treatment, 75% relief from symptoms after five days, and almost complete relief within nine days, including the normalisation of diabetes mellitus within 12 days using medicines such as Guduchi, *Ashwaganda Vati*, and *Pathyadi Kwath*; Yoga; dietary recommendations; and lifestyle modifications; along with MWM treatment [9]. Joshi and Puthiyedath, too, observed improvements in their patient within one day of administering Ayurvedic medicines *Shadangapaniyam*, *Shaddharana-curna*, *Sukshmatriphala*, *Kanakasavam*, and *Indukantam Kashayam*, along with MWM treatment [10]. Such improvements included breathing without difficulty and oxygen saturation stabilised at 95–98% up from 80%; within the next two days, the patient was asymptomatic without oxygen support and was thus discharged after a further seven days.

Such research follows other Ayurvedic investigations into the treatment of patients with breathing difficulties, such as those associated with bronchial asthma sufferers [11]. For example, in a large-scale survey of 100 studies, Gupta and Prajapati found evidence that patients with bronchial asthma, presenting with either *Shwasakastata* (breathlessness), *Kasa* (coughing), *Pinasa* (rhinitis), *Kanthodhwamsa* (throat irritation), or *Lalatesweda* (perspiration on the forehead), who were tested before and

after Ayurvedic treatment using herbal formulas such as *Vāsāvaleha*, significantly decreased in symptomatology after four weeks [12].

Jadav, Dave and Varsakiya also found a marked improvement in breathlessness, coughing, rhinitis, and chest pain (*Parshvashula*) after six weeks of *Shunthyadi Churna*, an Ayurvedic formula which contains *Pippali* and *Marchia* [13]. Recent considerations have also turned to the treatment of black fungus (*Mucormycosis*) using Ayurveda [14], and associations between comorbidities and COVID-19 mortality have been explored. For example, 47% of patients admitted to hospital in Delhi with COVID-19 were also diagnosed with diabetes mellitus, and diabetics have a lower survival rate than non-diabetics [15].

In order to further explore the association of Ayurveda on SARS-COV-2 infection, the following research question was posited to guide this study: Is the administration of Ayurvedic medicines associated with the survival rate of critically ill COVID-19 patients admitted to an intensive care unit in India?

MATERIALS AND METHODS

Research Context and Case Definition. This study was conducted at a Dedicated COVID Hospital (DCH) for admission to its intensive care unit (ICU) of critically ill patients with COVID-19 in India [16] at which the guidelines for the administration of COVID-19 treatment and care were provided [17]. Ethics approval for the research project was granted by the hospital and by the Ministry of AYUSH. A post-COVID-19 management protocol was issued by the Ministry of Health and Family Welfare [18]. The data of such cases who did not agree and who voluntarily agreed to receive additional Ayurveda treatment were recorded on a *pro forma* designed for this purpose [19]. Thus, for the present study, the early stage of the COVID-19 pandemic in India during 2020 was the *research context*; the DCH was the *case*; and study participants were the *embedded units of analysis*.

Case-Control Study Design. This study used the case-control study design defined by Robert Yin [20], as presented in Figure 1. A case-control study differs from a case study and observational study in that it covers "aggregated data, usually from a group of individuals who already have exhibited a…condition of interest", in this case the contraction of COVID-19. The case-control study design seeks to "estimate the statistical difference between the group's mean and the mean of the…'control' group" [20].

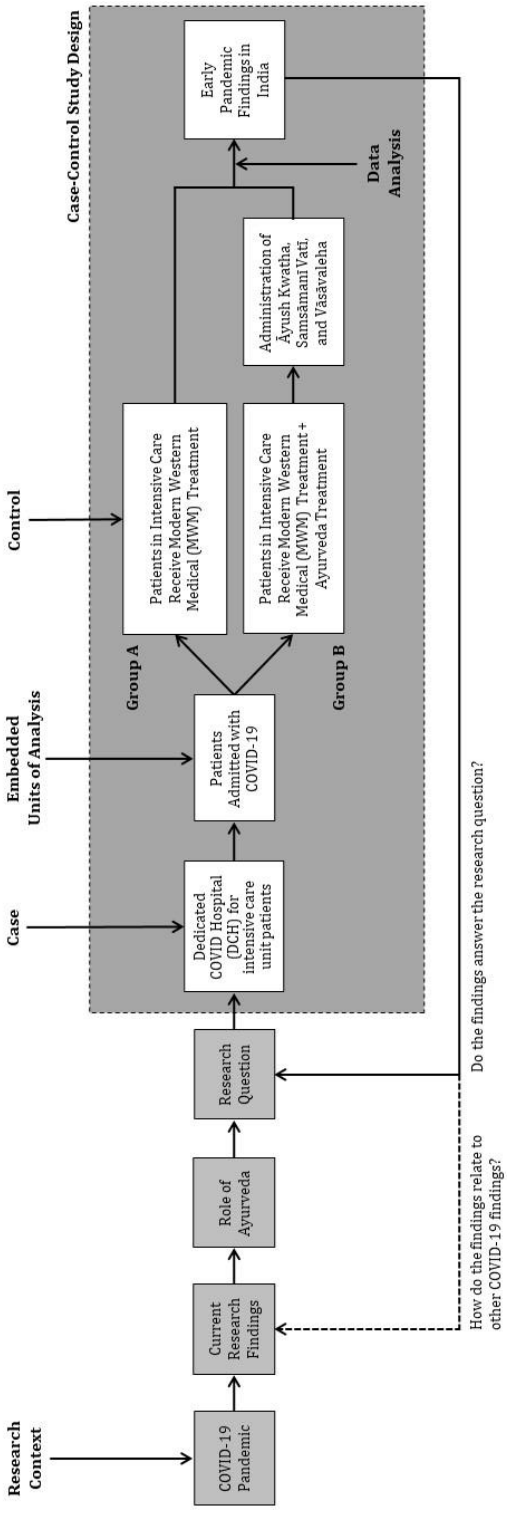

Figure 1: Research model of case-control study design.

Figure 1 shows that the research question for this study emerged from a consideration of the potential role for Ayurveda in treating critically ill patients admitted to hospital with COVID-19, in this case intensive care patients. The term 'critically ill' in this study means patients diagnosed as having severe pneumonia (with a respiratory rate ≥30/minute and/or SpO2 <90% in room air), or acute respiratory distress syndrome (ARDS), or septic shock [16]. These patients were given the option of receiving either: Group A—government-mandated, compulsory MWM treatment; or Group B—MWM along with Ayurvedic treatment. Findings from these two approaches of treatment were analysed in terms of the research question and their contribution to emerging knowledge about COVID-19.

Participants. As shown in Table 2, a total of 241 COVID-19-positive patients admitted between August and November 2020 were included in this study; 30% of patients were female and 70% were male.

Group A consisted of 110 patients treated in a separate ward, of which 33 (30%) were female and 77 (70%) were male; one patient (1%) was <15 years of age, 30 patients (27%) were between 16 and 40 years of age, 36 patients (32%) were between 41 and 59 years of age, and 42 patients (39%) were >60 years of age. Twenty-seven percent of Group A were also diagnosed with diabetes mellitus (DM), 39% with severe acute respiratory illness (SARI), and 35% with bronchial pneumonia (BP).

Group B consisted of 131 patients who consented to receive the additional Ayurveda treatment. Of this Group, 38 (29%) were female and 93 (71%) were male; four patients (3%) were <15 years of age, 19 patients (15%) were between 16 and 40 years of age, 63 patients (47%) were between 41 and 59 years of age, and 43 patients (33%) were >60 years of age, with three patients whose age was unknown at admission. Forty-five percent of Group B were also diagnosed with DM, 12% with SARI, and 44% with BP. Thirty-eight percent and 47% of patients in each Group, respectively, had other comorbidities or illnesses.

Procedure. Inclusion criteria for both Groups at presentation were critically ill, COVID-19-positive patients who had one or more of the following conditions and/or symptomatology: dyspnoea; pyrexia; hypertension (HT); DM; SARI; chronic obstructive pulmonary disease (COPD); BP; acute febrile illness (AFI); and/or other comorbidities, and who were subsequently admitted to intensive care. Patient inclusion criteria for Group B also included: consent to receive the adjunct Ayurvedic treatment along with MWM. The study size was determined by patients who met the inclusion criteria, thus matching of embedded units

of analysis in Group A 'controls' and in Group B 'treatment' occurred as a result of consent.

Table 2: Demographic data of Group A, treated with compulsory MWM, and Group B, treated with compulsory MWM and Ayurveda intervention.

Dimension		Group A		Group B		Average	
		Number	%	Number	%	Total	%
Gender	Male	77	70%	93	71%	170	70.5%
	Female	33	30%	38	29%	71	29.5%
	Total	110	46%	131	54%	241	100%
Age	Less than 15 years	1	1%	4	3%	5	2%
	16-40 years	30	27%	19	15%	49	21%
	41-60 years	36	33%	63	47%	99	40%
	More than 60 years	43	39%	42	33%	85	36%
Length of Stay in Intensive Care Unit (ICU)	Mean days	10.9	—	17.4	—	14.1	—
	SD	7.9	—	12.1	—	10.0	—
Comorbidities	Hypertension (HT)	27	25%	—	—	27	25%
	Diabetes mellitus (DM)	30	27%	59	45%	89	36%
	Severe acute respiratory illness (SARI)	43	39%	16	12%	59	25.5%
	Chronic obstructive pulmonary disease (COPD)	10	9%	7	5%	17	7%
	Bronchial pneumonia (BP)	39	35%	57	44%	96	40%
	Acute febrile illness (AFI)	6	5%	56	43%	62	24%
	Other	42	38%	62	47%	104	42.5%

All patients with acute respiratory distress syndrome (ARDS) were subsequently transferred to the ICU, and those experiencing severe hypoxemic respiratory failure received further treatment. On admission, patient data for age, gender, date of admission, date of death or discharge, symptomatology, and comorbidities, such as HT, DM, SARI, COPD, BP, AFI, dyspnoea, ageusia, myalgia, pyrexia, were recorded. Other diseases and/or illnesses were also diagnosed and recorded.

Intervention. At point of entry, the hospital followed MWM triage guidelines and protocols provided by the Ministry of Health and Welfare [16] for infection and prevention control (IPC) and early support therapy and monitoring for all patients in Groups A and B, including the use of appropriate personal protection equipment (PPE), supplemental oxygen therapy where necessary, conservative fluid management in patients with SARI, administration of empiric antimicrobials, close monitoring, and so on as applicable.

Table 3: Summary of Ministry of Health and Welfare protocol for stages of MWM treatment for all COVID-19 patients.

MWM Protocol	Example of Protocol
Immediate implementation of Infection Prevention Control (IPC) Measures	Personal protection equipment (e.g., triple layer surgical mask, eye protection, gloves, and gown), supplemental oxygen therapy where necessary, conservative fluid management in patients with SARI, administration of empiric antimicrobials, and close monitoring
Early supportive therapy and monitoring	Immediate supplemental oxygen therapy to patients with SARI and respiratory distress, hypoxaemia, and/or shock; conservative fluid management in patients with SARI; administration of empiric antimicrobials; and close monitoring
Collection of specimens for laboratory diagnosis	Relevant blood samples and nasopharyngeal and oropharyngeal swabs
Management of hypoxemic respiratory failure and ARDS	High-flow nasal catheter oxygenation or non-invasive mechanical ventilation; in the most extreme cases tracheal intubation and invasive mechanical ventilation
Management of septic shock	Antimicrobial therapy and fluid loading, and vasopressors for hypotension
Other Therapeutic Measures	Glucocorticoids for short periods of time; patients suffering from anxiety and fear supported by psychological counselling
Prevention of complications	Weaning protocols that include daily assessment for readiness to breathe spontaneously; minimising continuous or intermittent sedation; targeting specific titration endpoints or with daily interruption of continuous sedative infusions

At this time, relevant blood samples and nasopharyngeal and oropharyngeal swabs were taken. For all patients with ARDS, who were subsequently transferred to the hospital, and patients experiencing severe hypoxemic respiratory failure, in addition received further treatment, including high-flow nasal catheter oxygenation or non-invasive mechanical ventilation, and in the most extreme cases tracheal intubation and invasive mechanical ventilation. The details of MWM treatment are provided in Table 3.

Critically ill patients in Group B transferred to ICU were given Ayurvedic medicines as an add-on to MWM treatment. In addition to the standard interventions for COVID-19, patients in Group B received each (or a combination of each) of the following three Ayurvedic immunomodulator medications: 1) *Āyush Kwath* (आयुष क्वथ्); 2) *Samshāmanī Vatī* (संशमनी वटी); and 3) *Vāsāvaleha* (वासावलेह). The medications were administered as an 'add-on' to the MWM treatment under supervision of qualified Ayurvedic doctors in accordance with guidelines from the Ministry of AYUSH [1]. Medicines were manufactured and supplied by goods manufacturing practices (GMP) certified firms.

Āyush Kwath. Ayurvedic experts maintain that the antiviral and antibacterial properties of Āyush Kwath boost immunity. For example, due to the presence of eugenol, phenolic compounds, linoleic acid, and other compounds, Tulsi, a component of Āyush Kwath has "antimicrobial (including antibacterial, antiviral, and antimalarial properties), anti-diarrheal, anti-oxidant, anti-inflammatory, hepato-protective, cardio-protective, reno-protective, analgesic, antipyretic, and immune-modulatory properties and is thus recommended as a treatment for a range of diseases including features like cough, fever, asthma, anxiety", according to Gautam et al. [6]. Each 9 g of Āyush Kwath contains the following compounds: 4 g of dried Tulsi (तुलसी, *Ocimum sanctum*) leaves; 2 g of *Dālachini* (दालचीनी, *Cinnamomum zeylanicum*) stem bark; 2 g of dried *Sunthi* (शुण्ठि, *Zingiber officinale*) rhizome; and 1 g of the dried, unripened fruit *Kṛishna Marich* or black pepper (कृष्ण मरीच, *Piper nigrum*).

Samshāmanī Vatī. This herbal preparation has been successfully used in the treatment of diabetes mellitus [21]. Ayurvedic experts maintain that because of its medicinal attributes and genetic diversity, such as its anti-diabetic, anti-periodic, anti-spasmodic, anti-inflammatory, anti-arthritic, anti-oxidant, anti-allergic, anti-stress, anti-leprotic, anti-malarial, hepatoprotective, immunomodulatory, and anti-neoplastic properties, Samshāmanī Vatī is a worthy candidate for COVID-19 treatment. Each 250-milligram tablet of Samshāmanī Vatī is prepared

from an aqueous extract of the dried stem of Guduchi (गुडूची, *Tinospora cardifolia*), which in Ayurveda means 'that which protects the body from disease'. Guduchi has a variety of active components including "alkaloids, steroids, diterpenoid lactones, aliphatics, and glycosides [and these compounds] have been isolated from the different parts of the plant body, including root, stem, and whole plant" [22]. Indications for appropriate use of Samshāmanī Vatī include: *Jvara* (ज्वर, fever); *Jīrṇajvara* (जीर्णज्वर, chronic fever); *Daurbalya* (दौर्बल्य, general weakness); *Viśama Jvara* (विषमज्वर, irregular or intermittent fever); and *Pānduroga* (पाण्डुरोग, anemia).

Vāsāvaleha. Vāsāvaleha is one of several *Avaleha* (अवलेह, i.e., a linctus or cough mixture) used in Ayurveda for the treatment of various disorders [12] and as a *Rasāyana* (रसायन, i.e., as an immunomodulator). 10 g of Vāsāvaleha is prepared from the following: 7.6 g of dried *Vāsāka Śvarasa* (वासक स्वरस, *Adhatoda vasica*) leaves; 3.8 g of *Sita* (सित, sugar candy); 3.8 g of *Madhu* (मधु, honey); 0.95 g of *Ghrita* (घृत, clarified butter or ghee); and 0.95 g of dried *Pippali* (पिप्पली, *Piper longum*) fruit. Indications for appropriate use of Vāsāvaleha include: *Kasā* (कसा, coughing); *Śvasā* (स्वसा, breathlessness); *Jvara* (ज्वर, fever); *Pārshvashūla* (पार्श्वशूल, intercostal neuralgia and pleurodynia); and *Hritshula* (हृत्शूल, cardiac pain, i.e., angina pectoris).

Table 4 presents the Ayurvedic medicine, dose, *Anupāna* (i.e., substance used to aid the effectiveness of medicine), and duration of treatment for both non-diabetic and diabetic patients.

Table 4: Group B Ayurvedic medications for non-diabetic and diabetic patients.

Ayurvedic Medicine	Dose	Anupāna	Duration
Non-diabetic Patients			
Āyush Kwath	20 ml, once per day	Lukewarm water	28 days
Samshāmanī Vatī	2 tablets, three times per day	Lukewarm water	28 days
Vāsāvaleha	5 g, twice per day	Lukewarm water	28 days
Diabetic Patients			
Āyush Kwath	20 ml, once per day	Lukewarm water	28 days
Samshāmanī Vatī	2 tablets, three times per day	Lukewarm water	28 days

Data Analysis. To answer the research question, a binary logistic regression analysis [23] was performed to estimate the effects of four prognostic factors on the likelihood (odds) of survival versus non-survival for ICU patients with severe COVID-19: 1) Group; 2) Age; 3) Gender; and 4) Number of patient comorbidities. In this preliminary case-control study, the statistical relationship between prognostic factors and outcomes was assessed primarily for the purpose of estimating effect sizes (adjusted odds ratios or OR) to help plan a future expanded randomised controlled study.

The focus of the logistic regression analysis was to assess the determinants of successful survival, which was defined as sufficient recovery to qualify for release from the ICU. Thus, the dichotomous dependent variable in the logistic regression was coded as survival = 1, for patients who recovered, and non-survival = 0, i.e., those patients who died while in ICU. The dependent variable in the regression was the natural log of the odds of survival (logit), defined as $\ln[P/(1 - P)]$, where P is the probability of survival and $1 - P$ is the probability of non-survival.

The four independent variables in the regression equation were defined as: 1) **Group:** Group A = 0 and Group B = 1; 2) four categories of **Age:** ≤ 15 years = 1, 16–40 years = 2, 41–59 years = 3, and ≥ 60 years = 4, and which is treated as continuous in the regression; 3) **Gender**: male = 0 and female = 1; and 4) **Comorbidity** at the time of patient presentation to the hospital. Comorbidity was defined as the count of how many of seven different comorbidities were diagnosed in each patient: HT; DM; SARI; COPB; BP; AFI; and other (which included asthma, cardiogenic shock, CKD, hepatitis, hypothyroidism, and meningitis).

One diagnostic test for model adequacy (i.e., the Box-Tidwell test) required taking the natural logarithm of comorbidity so the variable was recentered by adding the value 1 for no comorbidity in order to avoid zero values. This modification did not affect the estimated magnitude or significance of the OR coefficients for comorbidity or other variables in the regression. Three patients in Group B whose age was unknown were omitted from the analysis. In addition, one patient from Group B was omitted from the sample to remove an outlier in the model residuals. The total data sample for the logistic regression analysis thus consisted of n = 110 for Group B and n =127 for Group B, total N = 237.

The logistic regression model was estimated using Stata 16 software. All key assumptions of the statistical analysis appear to be satisfied. First, in view of the study design, independence of observations for study participants seems to be a reasonable assumption. Second, when the count

variable for comorbidity was treated as approximately continuous, and the categorical variable age likewise was treated as continuous, the Box-Tidwell procedure [24] indicated this these predictors were linearly related to the log odds in the logistic regression model (p = .55 and p = .45, respectively). Third, after omitting the single outlier from the sample, the assumption of no extreme outliers was also satisfied. All standardised residuals were between +1.45 and –2.22 SDs.

RESULTS

A total of 30 patients out of 110 (27.2%) in Group A and 19 patients out of 131 (14.5%) in Group B did not survive COVID-19 infection. Table 5 provides the cross-tabulation data by Group and survival with column percentages. For logistic regression analysis, with the removal of three patients whose ages were unknown and one patient whose data were an outlier, Groups changed to 30/110 (27.2%) survival for Group A and 17/127 (13.3%) survival for Group B, resulting in $N = 237$.

Table 5: Crosstabulation data for survival frequency and percentages of Groups A and B.

Crosstabulation		**Group**		**Total**
		A	B	
Survival	No	*n* = 30	*n* = 17	*n* = 47
		27.2%	13.3%	19.8%
	Yes	*n* = 80	*n* = 110	*n* = 190
		72.8%	86.6%	80.1%
Total		*n* = 110	*n* = 127	*N* = 237
		100%	100%	100%

Table 6 reports the output for binomial logistic regression analysis. The logistic regression model was statistically significant as indicated by the omnibus Chi-square test of coefficients for all four predictors ($\chi^2(4) = 14.57$, $p < .006$). This is a test of the null hypothesis that the four predictors in the regression are all equal to zero.

The Hosmer-Lemeshow goodness-of-fit (GOF) test for the model was satisfactory ($\chi^2(8) = 7.49$, $p = .485$), as was the Pearson GOF test ($\chi^2(50) = 40.99$, $p = .814$). Both tests failed to reject the null hypothesis of good fit.

For each of the four predictors, Table 6 shows the estimated adjusted OR together with corresponding Wald tests, standard errors (SEs), *p*-values, and 95% confidence intervals (CI).

Table 6: Logistic regression results, including OR and probability values for each group, age, gender, and comorbidity.

					Number of observations = 237	
					LR Chi-square (4) = 14.57	
Log likelihood = –110.76					Probability > Chi-square = .006	
Survival	**OR**	**SE**	***z***	***P*>[*z*]**	**95% CI**	
Group	2.54	.87	2.71	.007	1.30	4.98
Age	.55	.13	–2.52	.01	.35	.88
Gender	1.13	.43	0.33	.74	.54	2.37
Comorbidity	.95	.16	–0.29	.77	.69	1.31
Constant	19.76	17.22	3.42	.001	3.58	109.01

Note: 'Constant' is the estimate of baseline odds, i.e., the predicted value Y when all X variables theoretically = 0.

The adjusted OR for patients in Group B was 2.54 with $p = .007$ for the two-tailed Wald test ($p = .006$ for the LR test). This indicates, on average, after adjustment for age, gender, and comorbidity, the odds for survival of ICU patients in Group B were 2.54 times larger than for those in Group A. Equivalently, the OR for Group B indicates an increase of 154% in the odds of survival compared to Group A of the same age, gender, and number of comorbidities. The 95% CI, however, is relatively wide.

Odds ratios can be converted to adjusted relative risk (or risk ratio [RR]) using a procedure implemented in Stata 16 [25]. The advantage of this conversion is that risk ratios are more readily interpretable by many clinicians and investigators compared to odds ratios. Corresponding to the adjusted OR for Group B of 2.54 is a relative risk of 1.20. This indicates that for two patients with the same age, gender, and comorbidity, patients in Group B have a 20% greater chance of survival than those in Group A.

The adjusted OR of .55 for age ($p = .009$ for the LR test) also indicates that an increase of one age category, on average, was associated with a decrease of 45% in the odds of survival after controlling for group, gender, and comorbidity. Thus, equivalently, an OR = .55 can be stated as a relative

risk of .82, indicating a decrease of 18% in the likelihood of survival for ICU patients.

Finally, the LR test *p*-values of .74 for the gender OR and .77 for the comorbidity OR, and the corresponding *p*-values for Wald tests in Table 6, indicate these data are consistent with the null hypothesis of no effect of gender or comorbidity on the odds of survival. Likewise, the relative risk for gender was 1.03 and for comorbidity .99, indicating that for females there was a 3% nonsignificant increase in the risk of not surviving for patients of the same group, age, and comorbidity and, for patients suffering from a comorbidity at presentation, the relative risk of .99 indicates that for patients of the same group, age, and gender, an increase of one additional comorbidity means a nonsignificant reduction of 1% in survival probability.

The model reported in Table 6 was also estimated using robust logistic regression. In the robust procedure, all estimated regression coefficients remain the same as those for standard ML estimation but reported SEs for model coefficients and tests of significance are robust to misspecification of the regression error term of unknown form [26]. In this case, the robust SEs and *p*-values were nearly identical to the standard ML values in Table 6.

A second sensitivity analysis examined the impact of including the outlying observation (patient ID = 177, referred to above) that was omitted from the analysis reported in Table 6. With this expanded sample ($N = 238$) the results of sensitivity analysis were similar to those reported in Table 6. The diagnostic tests for model adequacy were also satisfactory (with the exception of the outlying observation).

DISCUSSION

The purpose of this study, using a case-control study design, was to examine whether the addition of three Ayurvedic medicines to standard modern Western medical treatment was associated with the survival rate of critically ill COVID-19 patients admitted to an intensive care unit in India.

Worldwide data on the survival rate of critically ill patients with COVID-19 in ICUs at the time of this study indicated the outcome is conditional on setting. In the early stages of the COVID-19 pandemic, using a meta-analytic approach to 24 observational studies, including 10,150 patients identified from hospitals across Asia, Europe, and North America, Armstrong, Kane and Cook observed the survival rate for COVID-19

patients in ICU was less than 50% [27]. In a later review of 193 studies, including 43,128 COVID-19 deaths in intensive care units in 26 countries, Armstrong et al. found the average survival rate prior to May 2020 was about 58% but, as a result of changes to, and advances in, therapeutics and patient management while in intensive care, this percentage increased to about 65% later in 2020 [28].

Similarly, Contou et al. reported ICU COVID-19 survival rates of 52% [29], and Flythe et al. found the survival rate within 28 days of admission to ICU was less than 50% for patients with CKD but increased to 65% for those without [30]. However, Burrell et al. reported the COVID-19 survival rate at 77 ICUs in Australia was 85% [31]. Therefore, the survival rates observed in this study of Group A (72.8%) and Group B (85.5%), with an overall average survival rate of 79.1%, appear relatively high by international standards but are nevertheless largely consistent with the survival rate of ICU patients in some developed countries.

The observed difference in survival rate between the non-Ayurveda MWM only Group A and the MWM plus Ayurveda Group B is both statistically and practically significant. The finding that critically ill patients treated with both MWM and Ayurvedic medicines survived at a rate which is more than double the non-Ayurveda group, suggestive of a 154% increase in the odds of surviving COVID-19 or a 20% greater chance of survival, is noteworthy, thereby answering the research question in the affirmative.

This finding is also of interest given the percentage of patients over the age of 60 years in Group A was 72% but in Group B it was 80%, thus making Group B more vulnerable, as reflected in the relative risk. The degree to which the observed higher survival rate of Group B was due to a) improved base immunity and hence greater preventive power, b) improved acquired immunity as a result of the Ayurvedic medicines, c) the purely therapeutic effects of Ayurvedic medications on either the SARS-COV-2 virus or the COVID-19 disease itself, d) a combination of improved immunity and therapeutics, or e) other factor(s) yet to be identified remains to be explained by further investigation. As 'survival' in Group B was not controlled in this study, the question of 'cause' must remain a topic for future experimentation.

However, if Rajput is correct when he said "prevention of diseases by increasing immunity is of first priority [to Ayurveda] and [the] second priority is given to treating the disease" [32], then it may be that both improved base and acquired immunity (i.e., causes a) and b)) and a therapeutic effect of Ayurvedic medicine (i.e., cause c)), in that order,

affected the survival rate of patients in Group B. What is also not clear is whether each of the medicines prescribed to Group B—Āyush Kwath, Samshāmanī Vatī, and Vāsāvaleha—had equal individual 'effects' on the survival rate of critically ill patients or whether their combined use was important. Moreover, to test the immunity versus the therapeutic effect of Ayurveda, further experimentation related to dependent variables, such as serum counts for immunological cells and inflammatory markers as considered earlier by Sanger et al. [8], may be warranted in critically ill, rather than mildly ill, COVID-19 patients.

Generalisation. Given that patients in this study self-selected to receive the add-on Ayurvedic treatment, we can make no attempt at statistically generalising these findings to other clinical settings or to the wider national crisis then unfolding in India. Hence our focus on effect sizes and practical significance.

However, as Yin has pointed out, there is a difference between statistical generalisation and analytical generalisation [20]. Where the former attempts generalising data from a sample to a general population as a result of experimentation, the latter attempts generalising data from a case with embedded units of analysis to a theory as a result of, in this study, case-control. Mohajeri, Mesgari and Lee go further and point out there is also a difference between statistical significance and real-world usefulness [33]. Gaze and Collinson bridge these two ideas when connecting analytical generalisation and clinical, real-world significance [34]. Therefore, a consideration of analytical generalisation and real-world usefulness may be instructive in the present context.

Analytical generalisation. Yin explains the goal of analytical generalisation of case studies is to expand and generalise *theory* as distinct from statistical generalisation, which aims to extrapolate *probabilities* [20]. In this study we have sought the former by advancing analytical discussion of Ayurveda, namely: Are theories and historical accounts of infectious disease and immunity, as described in the ancient Vedic records of *Charaka Saṃhitā* (चरक संहिता) and *Sushruta Saṃhitā* (सुश्रुत संहिता), supported by evidence of survival rates in critically ill COVID-19 patients?

It is clearly not within the scope of this paper to analytically discuss every aspect of infectious disease (*Aupasargikaroga*, औपसर्गिकरोग) and pandemics (*Janapadoddhvaṃsanīya*, जनपदोद्ध्वंसनीय) nor the various approaches of Ayurveda in treating them, not is it possible to consider every aspect of a pandemic which Charaka Saṃhitā describes as 'a disease which can destroy a country' vitiated by 'deranged' environmental factors (*Vimānasthāna*, 3.6). But the underlying proposition guiding this research

was stated at the beginning: "good immune status is vital to prevention and to safeguard from disease progression" [1]. It is this discussion, and the attempt by this research to provide evidence of how to make patients' lives healthier and safer during the early stages of the pandemic, that analytically motivates our endeavour and from which we can approach the topic of relevance and real-world usefulness.

Relevance and real-world, clinical usefulness. Reliable data on hospital admission rates for COVID-19 patients were unavailable in India at the time of writing, particularly for the first six months of 2021 when infection rates surged. In 2020, Tseng et al. estimated hospital admission rates to be 6.0% for COVID-19 positive cases with a projected 670,000 patients hospitalised in Delhi [35].

Findings of Oliveira et al. in the U.S. at the time indicated approximately 10% of all patients admitted to hospital with COVID-19 were subsequently also admitted to intensive care [36]. Similarly, in Italy, Grasselli, Pesenti and Cecconi found 12% of patients admitted to hospital for COVID-19 were transferred to ICU during the same period, where 24% passed away (i.e., a 76% survival rate, with a 78.4% survival rate for those who were not placed on non-invasive or invasive mechanical ventilation versus a 73.5% survival rate for those who were) [37]. A survival rate of 76% in Italy is roughly the same as the 72.8% survival rate for Group A observed in our present study.

Thus, if it had held true that 10% of the estimated 670,000 hospitalised patients in Delhi infected with SARS-COV-2 also required intensive care (assuming enough ICU beds, equipment, and personnel were available to care for them at the same standard as provided at this hospital) with a survive rate of 72.8%, about 49,000 ICU patients would have been expected to recover from COVID-10 accompanied by about 18,000 who unfortunately would not. If this figure had been brought down by 14% through the use of Ayurvedic medicine as an add-on to MWM treatment, based on the case-controlled evidence derived from this study, approximately 2,500 intensive-care patients could be saved from death if Ayurveda was added to MWM treatment. This is the real-world clinical implication of the present finding.

CONCLUSION

In conclusion, binary logistic regression analysis offers empirical support that—after adjustments for age, gender, and number of comorbidities—the odds of survival of patients with severe COVID-19 who received

integrated Ayurvedic medicines in addition to mandated Western medical treatment were 2.54 times greater than those for patients who received the standard Western treatment protocol alone.

Thus, the Ayurveda patients had an increase of 154% in the odds of survival compared to patients of the same age, gender, and number of comorbidities. After adjustment for other prognostic factors, increased age was associated with a 45% reduction in the odds of survival, but gender and comorbidities were not significantly associated with changes in the odds of survival. It is recommended that further randomised control studies or pragmatic clinical trials be undertaken to further examine this phenomenon should the need arise in the future.

No reliable calculation can be made about the potential long-term benefits of Ayurveda and COVID-19 survival rates in India given limited data about infection rates, ICU rates, and survival rates of critically ill patients during the advancement of this pandemic. Nevertheless, we can infer practically, if not statistically, that if the survival rates observed in this study were experienced more widely, it follows axiomatically that a large number of critically ill COVID-19 patients might have benefitted (or might benefit in the future under similar circumstances) from the addition of Āyush Kwath, Samshāmanī Vatī, and Vāsāvaleha to modern Western medical treatment.

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