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ROLE OF CONVALESCENT PLASMA THERAPY IN PATIENTS WITH COVID-19 INFECTION- AN EXPERIENCE FROM A TERTIARY CARE CENTRE IN WESTERN U.P.

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Abstract:
Introduction: Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), the novel coronavirus that caused COVID-19 across the globe, originated in Wuhan, China. Due to the lack of definitive treatment options available for COVID-19 during the initial phase of the pandemic, researchers from around the world started to investigate the drug chain of events. Convalescent plasma was also used due to the domain-specific binding of antibodies to receptors resulting in its antiviral activity. Despite various RCTs, observational studies and case reports, there is unfortunately no clarity regarding its benefits in terms of overall efficacy and mortality outcomes for COVID-19.

Methodology: This is a case-control retrospective study conducted at GIMS, a tertiary care institute in Western Uttar Pradesh, India. Following ethical clearance, the study was carried out from April 1, 2020, to May 31, 2022. Patients with moderate to severe COVID-19 receiving plasma with standard therapy and ones only receiving standard therapy were taken as case and control groups respectively (ratio of 1:2). Exclusion criteria included critically ill patients, pregnant or lactating women, and individuals under 18 years of age. The final sample size was 174 patients after applying these exclusion criteria.
Result: The use of CP therapy reduces the mortality rate in COVID-19 patients as compared to standard treatment. The recovery rate was high among patients who received convalescent plasma in the age group of 30 – 50.
Conclusion: The convalescent plasma therapy may be more effective against newly emerging strains and could prove valuable as an alternative to more expensive treatment options. However, further study is needed to fully establish its efficacy and long-term outcomes.

Key words: COVID-19, Convalescent Plasma Therapy (CPT), SARS-CoV-2

Introduction:

COVID-19 is a highly infectious respiratory illness caused by a novel coronavirus and currently a big threat to global health. Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), the novel coronavirus causing COVID-19, originated from Wuhan, China and has spread rapidly across the globe [1]. Currently, there are no approved specific antiviral agents targeting the novel virus, while some drugs are still under investigation, including remdesivir and lopinavir/ritonavir [2]. Since the effective vaccine and specific antiviral medicines are unavailable, it is an urgent need to

look for an alternative strategy for COVID-19 treatment, especially among severe patients. Convalescent plasma (CP) therapy, a classic adaptive immunotherapy, has been applied to the prevention and treatment of many infectious diseases for more than one century. As no definitive treatment options are currently available for COVID-19, researchers all over the world have been investigating a variety of drugs like azithromycin, hydroxy-chloroquine, remdesivir, tociluzimab, anticoagulants and dexametha- sone [3–6]. Some of these are repurposed drugs and have been approved by regulators of various countries to be used as "Emergency Use Approval " (EUA) or "off label" medication [7]. Convalescent plasma (CP) has been used as a passive source of antibodies against various bacterial (tetanus and diphtheria) & viral diseases (poliomyelitis, measles, mumps) [8] and influenza A H1N1 [9]. CP was also considered in earlier pandemics of Spanish flu, West Nile Virus, Middle East Respiratory Syndrome (MERS), Severe Acute Respiratory Syndrome (SARS), and the more recent Ebola virus [10–12]. The convalescent plasma therapy (CPT) for COVID-19 has also been recently approved by US FDA and Indian Central Drugs Standard Control Organization [13]. It has been approved by the Ministry of Health and Family Welfare (MoHFW), Govt. of India, for "off label" use in patients with moderate and severe COVID-19 who are not improving and have increasing oxygen requirement despite use of steroids [7]. Evidence suggests that CP contains receptor binding domain specific antibodies which have potent antiviral activity [14,15]. Use of convalescent plasma is known to be well-tolerated with only a few easily managed adverse effects [16]. There have been, till date, few larger randomised controlled trials (RCT) [17,18], some retrospective observational studies [16,19,20] and many small case reports [21–23] indicating the benefits of CPT in COVID-19 patients with conflicting results. There is still not much clarity whether CPT offers mortality benefit and, if so, then in which category of COVID-19 patients.

Methods:

A case vs. control retrospective study was conducted for patients admitted at our hospital (GIMS; tertiary care institute, Western UP) from April 1, 2020 to May 31, 2022 after ethical clearance. Patients with moderate to severe COVID-19 receiving plasma with standard therapy and ones only receiving standard therapy were taken as Case and Control groups respectively (ratio of 1:2). The total sample size after excluding patients that were critically ill, pregnant / lactating, < 18 years turned out to be 174.

Inclusion criteria:

Case definition: Patients with moderate to severe disease who received CP along with standard treatment as per recommendations.

Control definition: Patients with moderate to severe disease who received only standard treatment as per recommendations.

Exclusion criteria: Incomplete data, Critically ill patients, pregnant & lactating females, and those <18 years old.

Statistical analysis: Continuous variables are presented as mean ± standard deviation (SD) or median with range, while categorical variables are presented as numbers and percentages (%). Student's t-tests have been used to compare the normally distributed data. We also used Chi-square test and Mann-Whitney test as per requirement. P value was calculated for significance< 0.05 was considered statistically significant. Regression models were used to assess risk factors. Binary logistic regression analysis was done to get an understanding of the various determinants that affect the probability of the outcome in different cases SPSS 21.00 software was used for the statistical analysis done

Results:

Clinical characteristics of the patients: 887 patients (174 convalescent plasma treatment group and 713 control group) were registered in this study. The comparison of patient characteristics between the cases and controls across various demographic and clinical factors is presented in Table 1.
The age distribution of patients is such that the younger age group (18-30 years) constituted only 6.32% of the cases but 31.3% of the controls, suggesting a lower likelihood of the outcome in this age group. At the same time, the older age groups (46-60 and >60 years) were over-represented among cases at 36.78% and 30.46% compared to 22.6% and 18.0% among controls; therefore, the likelihood of the outcome is higher with increasing age (Table 1 - Age distribution).

Males also form a significantly higher proportion of cases (76.44%) in comparison to controls (64.5%), while females constitute a lower proportion among cases (23.56%) than controls (35.5%). This implies a higher likelihood of the outcome in males (Table 1-Sex distribution).

The majority among both cases and controls are Hindus, at 95.40% of cases and 96.6% of controls, and a small percentage are Muslims at 4.60% of cases and 3.4% of controls. The religion distribution is relatively similar between the two groups (Table 1 - Religion). A larger proportion of cases 29.31% come from rural areas compared to controls 25.8%, while urban residents constitute 70.69% of cases and 74.2% of controls; therefore, the likelihood of the outcome is slightly higher in rural residents (Table 1- residential area).
Home admissions are predominant in both groups, but more so among cases at 93.68% compared to controls at 88.9%. Referral admissions are more common among controls at 11.1% compared to 6.32% among cases; therefore, cases are more likely to be admitted from home.(Table 1 - Admission type).

Distribution of blood group shows that the cases have a lower proportion of blood group A (24.14%) than controls (28.9%); blood group B is more frequent in cases (39.08%) than in controls (44.0%); significantly, blood group AB is higher in cases (26.44%) than in controls (18.9%), while the blood group O is almost equal in cases (10.34%) and controls (8.1%). (Table 1- Blood group)Age is a significant factor in which persons aged between 31-45, 46-60, and older than 60 years have significantly higher odds of about 2.5 times more than those aged between 18-30 years. Sex is also a factor, as females had significantly lower odds of about 0.595 than males. The blood group does not show a significant effect on the outcome (Table 2).

Persons referred from another facility had significantly lower odds of about 0.41 than those admitted from home (Table 2- Admission type). Table 2 morbidities show borderline significance of P=0.056. (Table 2 - Co-morbidity analysis) however, none of the other morbidity categories showed a significant effect on the outcome.
The condition's severity is a strong determinant; moderate and severe conditions significantly increase the (…??…..) about 8.556 and 20.174 when compared to mild conditions. Neither conventional therapy combined with Remdesivir nor Tocilizumab significantly altered the odds of the outcome compared to only conventional therapy (Table 2 - Treatment).
The severity of disease is significantly lower in cases, with younger groups (18-30) showing the strongest associations (OR = 0.035 and 0.032, respectively, both $p < .001$). Males (OR = 0.06) and females (OR = 0.072) also have a significantly lower risk of severe disease compared to controls (both $p < .001$). (Table 3).
Individuals with blood group AB exhibit the strongest association with reduced risk of severe disease (OR = 0.029, $p < .001$), followed by blood groups A, B, and O, all showing significant associations ($p < .001$). These findings highlight that younger age, males, and certain blood groups (particularly AB) are linked to a notably lower likelihood of severe disease (Table 3).

We looked at the clinical outcomes among different patient characteristics like age, sex, blood group and severity of disease by comparing cases with controls, including measures such as deaths, discharges, referrals, and DOPRs (Table 4).
For the 31-45 and >60 age groups, there are significant differences, with cases having higher death and referral rates compared to controls ($p = 0.004$ and $p = 0.001$, respectively,. Table 4)
Males show a noticeable difference in outcomes, with cases having lower discharge rates and higher referral rates than controls ($p = 0.000$). Blood groups A and B also exhibit significant disparities. Cases with blood group A have higher death rates and lower discharge rates ($p = 0.001$), while those with blood group B have higher referral rates ($p = 0.000$). Regarding disease severity, significant differences are observed particularly in mild and severe cases. Mild cases have higher death rates ($p = 0.001$), while severe cases have higher discharge rates with no deaths among cases compared to controls ($p = 0.000$) (Table 4).

We looked at conventional therapy alone, conventional therapy with Remdesivir, and conventional therapy with Tocilizumab and compared cases with controls (Table 5). For patients on conventional therapy alone, cases showed significantly higher death (2.5% vs. 0.3%) and referral rates (17.5% vs. 5.9%), and lower discharge rates (73.8% vs. 81.6%) than controls ($p = 0.001$). For those on conventional therapy with Remdesivir, cases had no deaths but still higher referral rates (14.9% vs. 3.0%) and lower discharge rates (82.8% vs. 88.7%) compared to controls ($p = 0.000$). Patients treated with conventional therapy plus Tocilizumab showed no significant differences in outcomes between cases and controls ($p = 0.172$), indicating similar effectiveness.
Our findings highlight significant differences in outcomes for the first two regimens, suggesting that cases generally fare worse than controls, except for those treated with Tocilizumab, where outcomes are comparable. (Figure:1).

Discussion:
The study investigates the efficacy of convalescent plasma (CP) therapy for COVID-19, particularly in patients with moderate to severe symptoms, amidst the global pandemic that began in Wuhan, China. The study registered 887 patients, with 174 in the CP treatment group and 713 in the control group, highlighting demographic and clinical characteristics.
In this preliminary study, age emerged as a significant factor, with older patients (31-60 years) exhibiting higher odds of severe disease than younger patients (18-30 years). Younger population, especially children have shown stronger innate immune reaction to SARS-CoV-2, especially in the nasal mucosa. This involves IFN signaling and the NLRP3 inflammasome which can rapidly control the spread of infection [24], [25]. While on the other hand, an older population can have an overactive, and often ineffective innate response, leading to a dysregulated pro-inflammatory cytokine production and tissue injury and thus increasing disease severity and higher mortality [26], [27]. Blood group distribution revealed that cases had a lower proportion of blood group A and a higher proportion of blood group AB compared to controls, suggesting potential associations with disease outcomes. A dose-dependent effect was seen between anti-B and of anti-A and susceptibility to SARS-CoV-2 in earlier studies as well [28].
Patients treated with conventional therapy along with remdesivir showed no deaths, indicating a potential positive impact on mortality rates when combined with convalescent plasma therapy. Remdesivir has been recognized and used as an antiviral drug against many diseases including COVID-19 [29] [30]. Here, we demonstrated that remdesivir, when used in conjunction with convalescent plasma therapy, resulted in higher referral rates and lower discharge rates compared to controls, suggesting a need for further investigation into its overall effectiveness, as also suggested in previous studies [31]. Remdesivir has been reported not to reduce RNA loads or detectability in SARS-CoV-2 but showed strong antiviral effects in preclinical models of infection with coronaviruses. Our study suggests that combining remdesivir with convalescent plasma therapy

may offer a complementary approach in treating COVID-19 patients, potentially improving outcomes and reducing mortality rates.

The findings suggest that younger age, male sex and specific blood groups are linked to a lower likelihood of severe disease, warranting further investigation into these associations. From the study of this small cohort of patients, it may be concluded that convalescent plasma therapy possibly reduces mortality rates in COVID-19 patients, particularly among those aged 30-50, and could be more effective against emerging strains. Despite these initial findings, the research highlights the need for larger studies to clarify the efficacy of CP therapy and its impact on mortality across different patient categories.

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Table 1: Demographic and basic clinical factors of patient groups on admission.

S.No	Character	Groups	Frequency		Percentage	
			Cases	Controls	Cases	Controls
1	Age	18-30 years	11	223	6.32	31.3
		31-45 years	46	201	26.44	28.2
		46-60 years	64	161	36.78	22.6
		>60 years	53	128	30.46	18.0
		Total	174	713	100	100
2	Sex	Male	133	460	76.44	64.5
		Female	41	253	23.56	35.5
		Total	174	713	100	100.0
3	Religion	Hindu	166	689	95.40	96.6
		Muslim	8	24	4.60	3.4
		Total	174	713	100	100.0
4	Resident	Rural	51	184	29.31	25.8
		Urban	123	529	70.69	74.2
		Total	174	713	100	100.0
5	Admission	Home	163	634	93.68	88.9
		Referral	11	79	6.32	11.1
		Total	174	713	100	100.0
6	Blood group	A	42	206	24.14	28.9
		B	68	314	39.08	44.0
		AB	46	135	26.44	18.9

O	18	58	10.34	8.1
Total	174	713	100	100.0

Table 2: The range of determinants that affect the probability of the outcome of patient groups on admission.

Variable		P value	Exp (B)	95% C.I. for Exp (B)	
				Lower	Upper
Age	18-30 (Ref)				
	31-45	0.021	2.459	1.144	5.287
	46-60	0.018	2.597	1.181	5.714
	>60	0.026	2.562	1.117	5.874
Sex	Male (Ref)				
	Female	0.027	0.595	0.376	0.944
Blood Group	A (Ref)				
	B	0.597	1.15	0.685	1.928
	O	0.081	1.693	0.937	3.058
	AB	0.083	1.982	0.915	4.294
Admission	Home (Ref)				
	Referral	0.025	0.41	0.188	0.893
Co Morbidity	No morbidity (Ref)				
	One morbidity	0.597	1.145	0.693	1.893
	Two morbidity	0.056	1.861	0.984	3.519
	Three morbidity	0.162	2.307	0.716	7.435
	Four morbidity	0.999	0.00	0.00	0.00
Severity	Mild (Ref)				
	Moderate	<.001	8.556	5.046	14.51
	Severe	<.001	20.174	12.167	33.448
Treatment	Only Conventional therapy (Ref)				
	Conventional therapy + Remdesvir	0.88	0.968	0.636	1.474
	Conventional therapy + Tocilizumab	0.158	0.469	0.164	1.341

Table 4: Clinical outcome of patients with different characteristics like age, sex, and blood group.

Table 3: The characteristics (age, sex, and blood group) of patients and their disease severity (mild, moderate, severe).

S.No	Characteristic	Groups		Mild		Moderate		Severe		Total		OR	95% Confidence Interval		p-valve
				n	%	n	%	n	%	n	%		Lower	Upper	
1	Age	<30 year	Cases	4	36.4	1	9.1	6	54.5	11	100.0	0.035	0.009	0.136	<.001
			Controls	210	94.2	10	4.5	3	1.3	223	100.0				
		30-50 year	Cases	6	13.0	11	23.9	29	63.0	46	100.0	0.032	0.012	0.08	<.001
			Controls	166	82.6	25	12.4	10	5.0	201	100.0				
		>50 year	Cases	12	18.8	26	40.6	26	40.6	64	100.0	0.113	0.056	0.23	<.001
			Controls	108	67.1	25	15.5	28	17.4	161	100.0				
		Total	Cases	12	22.6	10	18.9	31	58.5	53	100.0	0.148	0.071	0.31	<.001
			Controls	85	66.4	18	14.1	25	19.5	128	100.0				
2	Sex	Male	Cases	24	18.0	38	28.6	71	53.4	133	100.0	0.06	0.036	0.098	<.001
			Controls	362	78.7	56	12.2	42	9.1	460	100.0				
		Female	Cases	10	24.4	10	24.4	21	51.2	41	100.0	0.072	0.033	0.157	<.001
			Controls	207	81.8	22	8.7	24	9.5	253	100.0				
3	Blood group	A	Cases	7	16.7	9	21.4	26	61.9	42	100.0	0.047	0.019	0.113	<.001
			Controls	167	81.1	20	9.7	19	9.2	206	100.0				
		B	Cases	16	23.5	18	26.5	34	50.0	68	100.0	0.093	0.05	0.173	<.001
			Controls	241	76.8	46	14.6	27	8.6	314	100.0				
		AB	Cases	5	27.8	6	33.3	7	38.9	18	100.0	0.029	0.011	0.077	<.001
			Controls	48	82.8	4	6.9	6	10.3	58	100.0				
		O	Cases	6	13.0	15	32.6	25	54.3	46	100.0	0.08	0.023	0.276	<.001
			Controls	113	83.7	8	5.9	14	10.4	135	100.0				

S.	Character	Groups	Sample	Outcome										OR	95% Confidence Interval		p-value
				Deaths		Discharge		Refers		DOPRs		Total					
				n	%	n	%	n	%	n	%	n	%		Lower	Upper	
1	Age	18-30 years	Cases	0	0.0	10	90.9	0	0.0	1	9.1	11	100.0	1.32	0.162	10.734	0.951
			Controls	0	0.0	197	88.3	1	0.4	25	11.2	223	100.0				
		31-45 years	Cases	1	2.2	38	82.6	6	13.0	1	2.2	46	100.0	0.933	0.399	2.18	0.004
			Controls	0	0.0	168	83.6	8	4.0	25	12.4	201	100.0				
		46-60 years	Cases	0	0.0	52	81.3	8	12.5	4	6.3	64	100.0	0.615	0.281	1.345	0.526
			Controls	1	0.6	141	87.6	13	8.1	6	3.7	161	100.0				
		>60 years	Cases	1	1.9	37	69.8	14	26.4	1	1.9	53	100.0	0.561	0.27	1.166	0.001
			Controls	4	3.1	103	80.5	8	6.3	13	10.2	128	100.0				
2	Sex	Male	Cases	2	1.5	101	75.9	25	18.8	5	3.8	133	100.0	0.538	0.335	0.865	0.000
			Controls	3	0.7	393	85.4	21	4.6	43	9.3	460	100.0				
		Female	Cases	0	0.0	36	85.7	3	7.1	3	7.1	42	100.0	1.233	0.454	3.347	0.449
			Controls	2	0.8	216	85.4	9	3.6	26	10.3	253	100.0				
3	Blood group	A	Cases	1	2.4	33	78.6	7	16.7	1	2.4	42	100.0	0.506	0.217	1.182	0.001
			Controls	0	0.0	181	87.9	8	3.9	17	8.3	206	100.0				
		B	Cases	1	1.5	52	76.5	12	17.6	3	4.4	68	100.0	0.544	0.286	1.034	0.000
			Controls	3	1.0	269	85.7	11	3.5	31	9.9	314	100.0				
		AB	Cases	0	0.0	13	72.2	4	22.2	1	5.6	18	100.0	1.085	0.43	2.736	0.139
			Controls	0	0.0	46	79.3	4	6.9	8	13.8	58	100.0				
		O	Cases	0	0.0	39	84.8	5	10.9	2	4.3	46	100.0	0.678	0.202	2.278	0.319

			Controls	2	1.5	113	83.7	7	5.2	13	9.6	135	100.0					
4	Severity	Mild	Cases	1	2.9	29	85.3	3	8.8	1	2.9	34	100.0	0.867	0.325	2.31	0.001	
			Controls	1	0.2	495	87.0	11	1.9	62	10.9	569	100.0					
		Moderate	Cases	1	2.1	37	77.1	6	12.5	4	8.3	48	100.0	0.439	0.167	1.154	0.405	
			Controls	1	1.3	69	88.5	5	6.4	3	3.8	78	100.0					
		Severe	Cases	0	0.0	71	77.2	19	20.7	2	2.2	92	100.0	1.578	0.775	3.212	0.000	
			Controls	3	4.5	45	68.2	14	21.2	4	6.1	66	100.0					

Table 5:The assessment of patient outcomes like deaths, discharges, referrals, DOPRs under different drug regimens

S.No:	Drugs	Sample	Outcome										OR	95% Confidence Interval		p-value
			Deaths		Discharge		Refers		DOPRs		Total					
			n	%	n	%	n	%	n	%	n	%		Lower	Upper	
1	Conventional therapy	Cases	2	2.5	59	73.8	14	17.5	5	6.3	80	100.0	0.633	0.357	1.122	0.001
		Controls	1	0.3	262	81.6	19	5.9	39	12.1	321	100.0				
2	Plasma therapy +	Cases	0	0.0	72	82.8	13	14.9	2	2.3	87	100.0	0.609	0.32	1.16	0.000
		Controls	3	0.8	323	88.7	11	3.0	27	7.4	364	100.0				
3	therapy + R	Cases	0	0.0	6	85.7	1	14.3	0	0.0	7	100.0	1.000	0.094	10.66	0.172
		Controls	1	3.6	24	85.7	0	0.0	3	10.7	28	100.0				

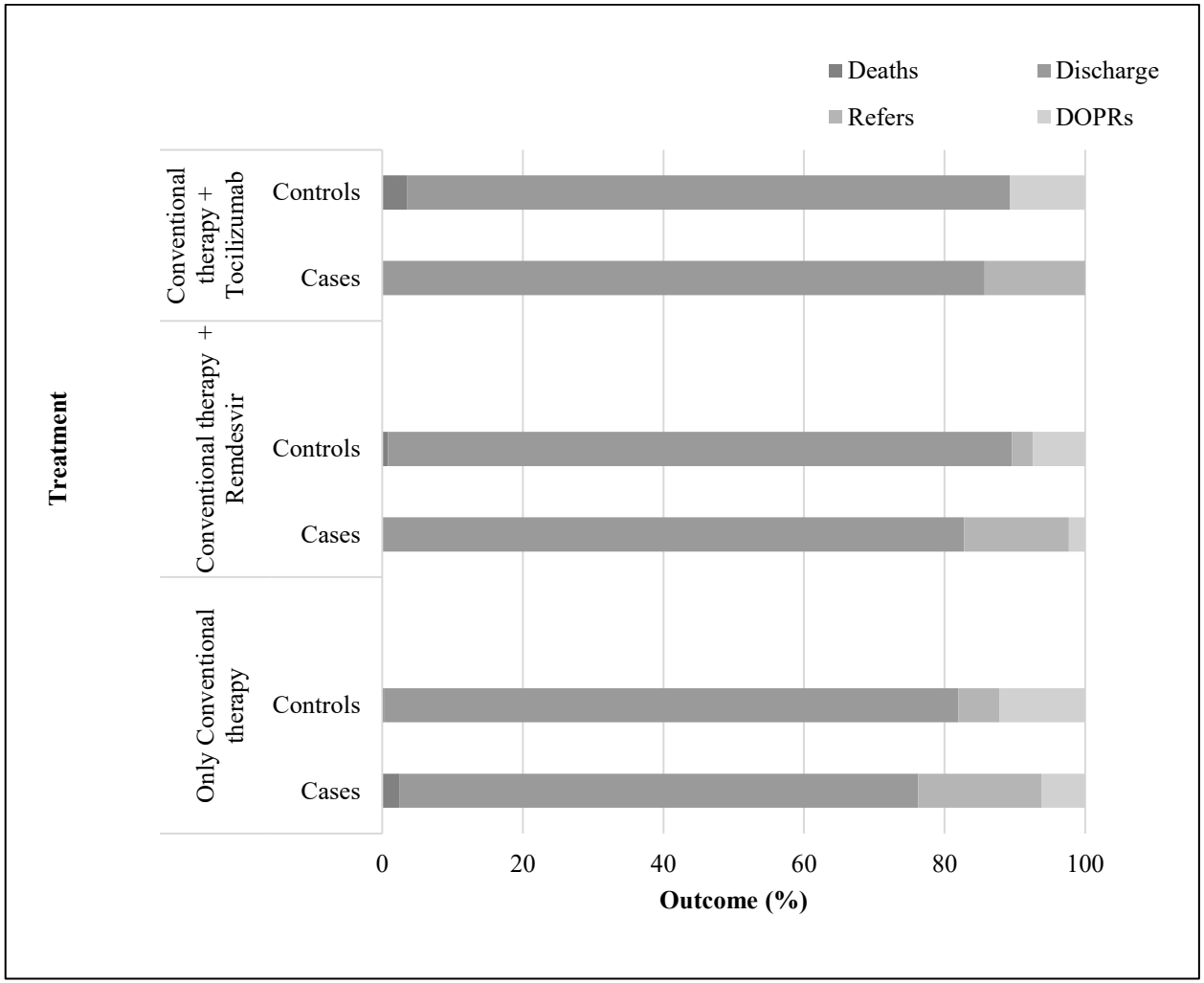

Figure 1: The clinical outcomes like deaths, discharges, referrals, DOPRs under different drug regimens.

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