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Systematic Review Article

Interpreting Kaplan Meier's survival curve in COVID-19 patients: a systematic review

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ABSTRACT

Covid 19 is the causative agent of coronavirus disease in 2019-2020; was declared a pandemic by the World Health Organization on 11th March 2020. The article aims to interpret the functionality of Kaplan Meier's survival curve used in various study designs. The search strategy and selection of published works in the MEDLINE database from the National Library of Medicine (NLM) was used to identify original journal articles published in English from March 1, 2020 to September 11, 2020. The search strings in title/abstract were 'COVID-19' or 'coronavirus' or and 'Kaplan Meier curve' that yielded 225 articles. Finally only 28 articles were reviewed. These were clinical trials (N=1), and retrospective (N=10) and prospective (N=1) observational studies (N=2), case control study (N=1) retrospective cohort study (N=6), medical record based study (N=3), observational studies (N=2), not specified (N=1), diagnostic test (N=1). 88% of articles were from China. Kaplan Meier's curve was depicted in all the studies and 17 were found to be highly significant for KM curve, 2 were found significant as 6 were found to be non significant and in 3 no mention of significance of p value was given. It was concluded that it is the first systematic review to date related to interpreting Kaplan Meier's survival curve in patients with COVID-19. The graph has been used singularly, in multiples and cumulatively, thus giving visual assessment which enhances the interpretation of results for survival analysis, failure to time and time to event plots. It is not only used in RCT study designs but a range of observational and retrospective studies.

Keywords: COVID-19, Interpretation, Kaplan Meier's survival curve, Significance, Study design

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the causative agent of coronavirus disease 2019 (COVID-19), which was declared a global pandemic by the World Health Organization (WHO) on 11th March 2020. SARS-CoV-2 was discovered in December 2019 in Wuhan City, Hubei Province, China.[1] One of the characteristics of COVID-19 is that it is highly contagious; China and 214 other countries have been affected in less than7 months. As of October 2020, the total worldwide confirmed cases was 43,341,451 with 1,15,7509 deaths and with 218 countries areas and territories affected (WHO).[2] We examine the fundamental concepts behind using a Kaplan Meier curve in various tudies. And its applicability to arrive at comprehendable conclusions for Health care practicitoners. Finally, we discuss the utility of the curves and thoughts regarding lessons for future analysis. When Kaplan Meier needs to be understood in the contexts of the types of analysis it allows, the outcomes in our medical literature in patient populations is important. It's the differences in outcomes like mortality rates in various subjects. Many health care workers may not be interested only in the Outcomes but time to the event. Time to the event analysis in oncology literature is the time taken for the patient after treatment

A versus treatment B. In orthopedics it can be time duration taken to replace or repair prosthesis A versus prosthesis B do we evaluate time to event. In most parts medical literature uses Kaplan Meier's curve. The components of the Kaplan Meier's survival curve, y-axis, which indicated the survival and the x-axis, which indicates the time trend. The KM is constructed y-axis against x-axis. An event is when the curve stops at an interval and the proportion of patient number is calculated. The KM also gives us the concept of cumulative probability which indicates probability of patients survived in the previous interval and made it to the current interval and then the numbers that made it to the next interval. KM also tells us about censoring which means that something has happened to the patients aside from suffering an event. Censoring has influence on estimating effects. The use of data as long as the patient is available after which this estimate becomes less precise. At risk group will be reduced from survival data. Including all the censored participants will be overestimating the patient survival and the more patient data one loses less accurate becomes the estimate. At the end of collection of patient data all patients are censored, whether they die on the next day or live for 10 years after the completion of the study. So when we look at the cumulative probability of survival it is the part of patient time. KMC gives estimate of two groups in which many things can be compared. We can calculate median survival or 50th percentile. We can compare treatment versus control and the 5 year survival or 3 year survival when plotted x-axis to y-axis.

It should also be noted that steeper the curve of the Kaplan Meier analysis worse is the prognosis in regards to the event of interest comparing KMC with survival data between two groups one has to look at the series of time points, analysis technique must consider the entire curve and the difference between the curves must be quantified with two measure like the log rank test which tell us the difference between groups that's statistically significant and the Hazard ratio which provides relative event ratio between two groups, HR<1 means treatment reduces the risk of event occurring, HR>I treatment increases the risk of event occurring and HR=1 treatment has no impact on the risk of event.[3] The curves when used need to be understood with a few key points. Censored data can substantially affect the KM curve, but have to be included when fitting the model. One has to be cautious when interpreting the end of the KM if there are big drops present, especially near the end of the study. This usually means that there are not a lot of people at risk (and the 95% CI intervals are broader). The height of the drop can inform you about the number of patients at risk, even when it's not reported or when there are no confidence intervals shown.[4] The interpretation of the survival curve is quite simple, the y-axis represents the probability that the subject still has not experienced the event of interest after surviving up to time t, represented on the x-axis. Each drop in the survival function (approximated by the Kaplan-Meier estimator) is caused by the event of interest happening for at least one observation.[5]

This is the first systematic review to date related to interpreting Kaplan Meier's survival curve in patients with COVID-19. Only 28 studies were eligible for inclusion for the time period March 1, 2020 to September 11, 2020. , most of which were conducted in China. Most of the KM curves were significant for the study of concern.

It is essential to do the overview because in our search for understanding application of various graphs and curves used. It was necessary to review a few studies which used Kaplan Meier's curves to make us understand the importance of survival index due to an intervention. Most times it is understood that KM curves are utilized only in RCT study designs but on reviewing many studies this presumption has been brought to a major paradigm shift to the concept. Aim and objective was to interpret and understand the functionality of Kaplan Meier's survival curve used in various study designs.

METHODS

The Study search strategy and selection of published works in The MEDLINE database from the National Library of Medicine (NLM), Pubmed PMC was used to identify Original Journal articles published in English from March 1, 2020 to September 11, 2020. The search strings in title/abstract were 'COVID-19' or 'coronavirus' or and 'Kaplan Meier curve' that yielded 255 articles. The search terms included combinations of: COVID 19 and Kaplan Meier's survival analysis curve. There were no restrictions on the types of study design or inclusion.

Search methods for identification of reviews All searches and screening were done independently by two authors (LT, SP) using the preferred reporting items for systematic reviews and meta-analyses statement (PRISMA) recommendations. The titles and abstracts were screened, based on the purpose of our review, and resulted in the exclusion of article. A total of 28 articles met the criteria for our systematic review and were included as shown in Figure 1.

Literature search the following databases were reviewed for published studies prior to September 20, 2020: PubMed, Google Scholar. Only printed articles were searched and no effort was put into searching for preprint as the search in print gave us ample case studies using Kaplan Meier's survival curve. Boolean logic was used for conducting database search and Boolean search operators "AND" and "OR" were used to link search terms. The following search strategy was adopted: COVID-19 AND 'Kaplan Meier curve'. Titles, abstracts, and full text were screened to ensure they met eligibility criteria. Two authors (LT and SP) screened scrutinized, retrieved, and excluded reports. Additional investigator (AS) was consulted in clearing doubts that arose during

the review process. (JN) helped with statistical procedures.

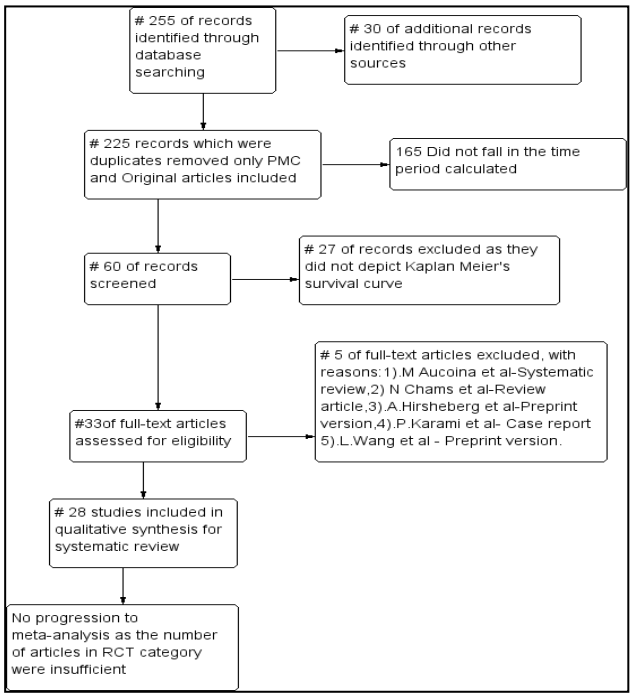

Figure 1: Prisma flow diagram.

Search strategy and selection criteria was done through Literature search in the PubMed, and NLM Library from March 1, 2020 to September 11, 2020. Using a combination of the following keywords: "COVID19" and Kaplan Meier's survival curve. Restrict publication language to English. In addition, to ensure the comprehensiveness and accuracy of the research, we also consulted the references of the included literature. This work was independently completed by two authors (LT and SP). Disagreements were resolved by the third investigator (AS). All the search results were evaluated according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.

Inclusion criteria

In the Eligibility criteria we included studies that were mainly in English and which reported on covid 19. Data was manually extracted and immediately tabulated from eligible studies by the investigators. The following variables were included: first author, type of design, site of study, year of publication, published journal or pre-print server, sample size, Kaplan Meier's curve. This did not include conference and pre-print publications.

Exclusion criteria

We excluded all review articles, hypotheses papers, editorials, case reports and case series.

Selection of reviews was done by the inclusion criteria of the systemic-analysis were as follows: (1) patients diagnosed with COVID-19 were included into the study, (2) involving the death group or non-survivor group and the survivor group, (3) Kaplan Meier survival graph should be depicted in study. Studies that were excluded were (a) repetitive publications, (b) editorials, case reports, letters, reviews and ecological studies, and (c) studies with fewer than five cases.

RESULTS

In Figure 2 the 28 articles, in the study, China, which had the maximum representation (13) 45 percent, France (2) seven percent, Japan (1) four percent, Italy (3) ten percent, Korea (2) seven percent, Spain (3) ten percent, USA (3) ten percent, Turkey (1) 4 percent. Of the 28 studies included in this review the types of studies were clinical trials (N=1), and retrospective (N=10) and prospective (N=1) observational studies (N=2), case control study (N=1) retrospective cohort study (N=6), MEDICAL record based study (N=3), observational studies (N=2), not specified (N=1), diagnostic test (N=1).

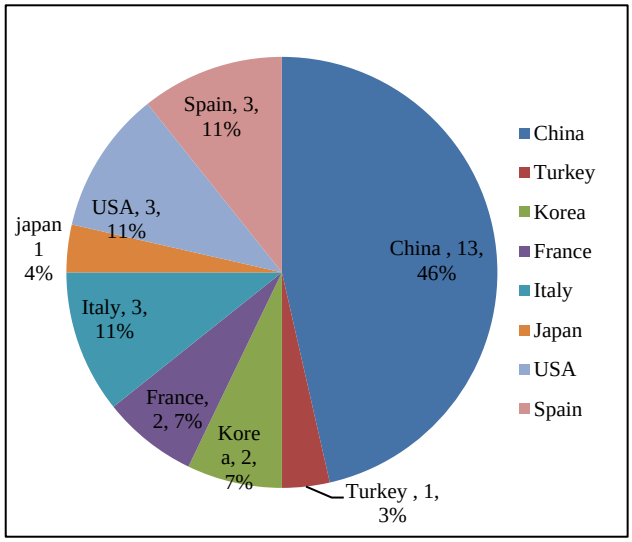

Figure 2: Countries represented in the present study.

In Table 1 the average age of the populations studied was 59.07 years. Sample size calculated in this study was 34445, (Thirty four thousand, four hundred and forty five) the maximum sample size was taken by Zhang et al with 13982 and the least number of Sample size was in a study by Zhang et al with 28 study subjects.[32,33]

Not mentioned denoted that no calculation of p value was made in three studies out of twenty eight. Out of the 28 studies survival analysis (20), 71.4 percent, failure time analysis (1), 3.7 percent, time to event (7), 25 percent. The articles published were between the time period of March 2020 to September 2020.

Table 1: Age and sample size distribution.

Author	Country	Sample size	Median age	Age significance
Baycan et al[7]	Turkey	100	Non sev. 53.7±15.1, 58% sev. 59.1±12.9	p<0.001
Bernabeu-Wittel et al[10]	Spain	272	87 (81-91) female	Not mentioned
Cao et al[11]	China	244	Mod 59.79±13.49 sev. 62.20±13.43 critical 68.98±11.26	p <0.001
Cheng et al[14]	China	305	Suvivors 63.0 (49.0-69.0) non surv 71.0 (63.0-78.0) Total 65	p<0.0001
Choi et al[40]	Korea	293	Progression 49.5 (34-57) improv 27 (23-46) Total 29	p <0.001
Campioli et al[42]	USA	251	Ambulatory 47 (27) hospitalized 60 (16.8) Total 53 (27)	p <0.001
Davido et al[36]	France	132	First period 62.17±15.24, second pd. 57.59±16.64	p<0.13
De Rossi et al[34]	Italy	158	Controls 71 (14.6) tocilizumab 62.9 (12.5) -3.706	p<0.001
Francone et al[15]	Italy	130	63.2±15.8, range 27-90 years) >75 years death significant	p=0.0083
Gao et al[17]	China	54	NT-proBNP≤88.64 pg/ml 51.6±13.9 NT-proBNP>88.64 pg/ml 67.4±14.4 Total 60.4±16.1	p<0.001
Green et al[44]	USA	3432	Repeat tested 59.9, single tested 53.4	p<0.001
Hou et al[45]	China	52	Not mentioned	Not mentioned
Jang et al[18]	Korea	110	critical 66.1±10.0 non critical 55.4±17.4, total 56.9±17.0	p=0.002
Adrien Joseph et al[53]	France	100	non AKI 54 (45–61) AKI 60 (54-68) total 59 (53-67)	p=0.05
Hiroshi Kamijo et al[54]	Japan	3195	Nafamostat 70 (62, 78) conventional 70 (60, 79) 0.066, overall 70 (61, 78)	p=0.066
Lagier et al[47]	France	3737	Mean age of 45.3±16.8 years	Not mentioned
Jeong-Hoon Lim et al[55]	Korea	164	Non Aki 67.0 (24.0-92.0) all AKI 75.0 (60.0-98.0) sig stg 3AKI	p=0.003
Liu et al[19]	China	1190	Survivor 56 (46, 65) non surv 69 (62, 77) all 57 (47, 67)	p<0.0001
Lovinsky-Desir et al[21]	USA	1298	no asthma 52 (21) asthma 51 (27)	p=0.26
Meng et al[50]	China	3232	cancer 61.7 (16.1) years, non cancer 57.9 (15.9) years	p=0.015
Shang et al[23]	China	584	59 years (interquartile range 25-75) older diabetic more affected	p<0.001
Uribarri et al[24]	Spain	758	EGFR>60 ml 61±17 EGFR 30-60 ml 78±11 EGFR<30 ml 79±13 mean 66.1	p<0.001
Wan et al[26]	China	123	Mild 43, severe 65	p<0.0001
Wang et al[28]	China	228	control 45.5 (36.0-60.8) all patients 45.5 (36.0-60.8)	p=1.000
Wu et al[30]	China	201	51 years (interquartile range, 43-60 years) ARDS patient were older	p<0.001
Yang et al[52]	China	93	Non severe 42.1±18.6, severe 57.9±11.8, total 46.4±17.6	p=0.034
Zhang et al[32]	China	28	Median 65.0 (56.0-70.0)	p=0.509
Zhang et al[33]	China	13981	Statin 66.0 (59.0-72.0) nonstatin 57.0 (45.0-67.0)	p<0.001

Table 2: Study types of Kaplan Meier's parameters.

Author	Type of study	Sample size	Type of KMC	KM significance	KM analysis	Journal	Year of publication
Baycan et al[7]	case control study	100	The parameters affecting mortality were evaluated by including LV-GLS and RV-LS in the two models separately	none	Survival analysis	The International Journal of Cardiovascular Imaging	20-Jun-20
Bernabeu-Wittel et al[10]	comparative cohort study	272	Cumulative survival during follow-up according to risk groups of PROFUND and CURB-65 indices	p=0.01	Survival analysis	Archives of Gerontology and Geriatrics	25-Aug-20
Cao et al[11]	retrospective observational study	244	Plot for survial past hospital admission stratified by hs-cTnI levels.	nm	Survival analysis	Theranostics 2020	29-Jul-20
Cheng et al[14]	retrospective single-centre study	305	Survival estimates according to blood urea nitrogen (BUN) and D-dimer levels.	nm	Survival analysis	International Journal of Antimicrobial Agents	19-Jul-20
Choi et al[40]	retrospective cohort study	293	Survival Analysis of progression-free survival : according to lopinavir/ritonavir treatment for patients with COVID-19	p not significant	Time to event	Journal of Clinical Medicine	23-Jun-20
Campioli et al[42]	retrospective cohort study	251	The median time from symptom onset to the first positive PCR test	p not significant	Time to event	Journal of Clinical Virology	03-Aug-20
Davido et al[36]	retrospective single-centre	132	Unfavorable outcome according to biological parameters (Kaplan-Meier	p=0.009	Failure time	International Journal of Antimicrobial Agents	01-Sep-20

Continued.

Author	Type of study	Sample size	Type of KMC	KM significance	KM analysis	Journal	Year of publication
	study		curves)Patients who benefited from AZI ±HCQ with CRP ≥100 mg/l were less likely to have an unfavorable outcome compared with patients with no treatment		analysis		
De Rossi et al[34]	retrospective cohort study	158	Survival curve for tocilizumab and control group showed a significantly greater survival rate of tocilizumab patients as compared to controls.	p<0.001	Survival analysis	EClinicalMedicine	17-Jul-20
Francone et al[15]	retrospective analysis single centre	130	The relationship between CT score and all-cause mortality, which were compared with the log-rank test	p<0.0001	Survival analysis	European Radiology	12-Jun-20
Gao et al[17]	retrospective, observational clinical trial	54	Cumulative survival curves of in-hospital death were estimated	p<0.001	Survival analysis	Respiratory research	12-Jul-05
Green et al[44]	medical record based	3432	Eestimate the conversion rate by day of testing with the following assumptions	nm	Time to event	Journal of Clinical Microbiology	23-Jul-20
Hou et al[45]	diagnostic test	52	Kaplan-Meier curve of CRISPR-COVID positive rate by CRISPR and PCR	p<0.05	Time to event	Plos pathogens	27-Aug-20
Jang et al[18]	retrospective study	110	cumulative risk of 28-day mortality according to the NEWS stratification	p<0.001	Survival analysis	J Korean Med Sci	16-Jun-20
Adrien Joseph et al[53]	retrospective monocenter study	100	Were used to express the probabilityof death from inclusion to day 28.	p=0.013	Survival analysis	Annals of intensive care	12-Jul-20
Hiroshi Kamijo et al[54]	retrospective cohort study	3195	Survival curves of the two groups were plotted with interval-censored data, and survival times were compared between the two groups using log-rank tests.	p=0.011	Survival analysis	Journal of Clinical Medicine	13-Aug-20
Lagier et al[47]	retrospective study	3737	Estimates show that the proportion of patients with positive PCR 10 days after inclusion was significantly lower among patients treated with HCQ-AZ	p<0.05	Time to event	Travel Medicine and Infectious Disease	14-Jun-20
Jeong-Hoon Lim et al[55]	retrospective study	164	30-day mortality was significantly higher in the stage 3	p<0.001	Survival analysis	Journal of Clinical Medicine	03-Jun-20
Liu et al[19]	single-center, retrospective, observational study	1190	To explore whether a specific antiviral agent was independently associated with prolonged survival	p<0.001	Survival analysis	Annals of intensive care	12-Aug-20
Lovinsky-Desir et al[21]	medical record based	1298	Curve demonstrating no significant difference in hospital length of stay between patients with (N 5 163) and without (N 5 1135) asthma.	p not significant	Survival analysis	J ALLERGY CLIN IMMUNOL	Jun-20
Meng et al[50]	retrospective study	3232	Displays the Kaplan-Meier curve for the length of hospital stay for discharged patients.	p not significant	Time to event	Journal of haemtology and oncology	Apr-20
Shang et al[23]	retrospective cohort study	584	Kaplan-Meier survival curve showed that COVID-19 patients with diabetes had a shorter overall survival time.	p<0.01	Survival analysis	The american journal of medicine	May-20
Uribarri et al[24]	medical record based	758	Kaplan-Meier survival landmark analysis according to the glomerular filtration rate.	p<0.001	Survival analysis	Journal of Nephrology	22-Jun-20
Wan et al[26]	Not Specified	123	Significant difference in survival rate between the mild and severe groups.	Nm	Survival analysis	British Journal of Haematology	22-Mar-20
Wang et al[28]	retrospective study	228	COVID-19. Patients with low HDL-C showed a higher risk of developing severe events compared with those with high HDL	p=0.009	Survival analysis	Lipids in health and disease	May-20
Wu et al[30]	retrospective cohort study	201	Among the patients with ARDS, of those who received methylprednisolone treatment, 23 of 50 (46.0%) patients died, while of those who did not receive	p=0.003	Survival analysis	JAMA Internal Medicine	11-May-20

Continued.

Author	Type of study	Sample size	Type of KMC	KM significance	KM analysis	Journal	Year of publication
			methylprednisolone treatment, 21 of 34 (61.8%) died.				
Yang et al[52]	retrospective study	93	To identify the factors that affect COVID-19 progression, eight potential factors were included in the analysis by using the Kaplan–Meier curve and the univariate Cox regression model.	p<0.001	Time to event	International Immunopharmacology	Apr-20
Zhang et al[32]	retrospective study	28	The adjusted survival curve of severe events showed that cancer patients who underwent antitumour treatment in the past 14 days or had patchy consolidation in CT on admission had significantly higher severe events.	P¼ 0.010	Survival analysis	annals of oncology	26-Mar-20
Zhang et al[33]	retrospective study	13981	The association between statin usage and 28-day all cause death was calculated with an adjusted HR of 0.58 (95% CI, 0.43-0.80) compared to non-statin group.	p=0.001	Survival analysis	Clinical and Translational Report	04-Aug-20

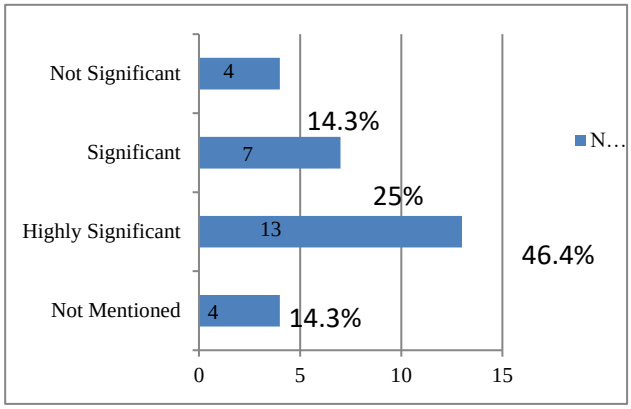

Figure 3: Significance of Kaplan Meier's curve

Figure 3 shows study for age in which 3 out of twenty eight studies were very highly significant age with p value <0.0001 and highly significant were fourteen with p values between <0.001 to <0.0083. Only 2 studies were significant for age at p<0.05, 6 studies did not show significance for age. 3 out of twenty eight studies did not mention any calculation for age.

Figure 3 depicts that the significant finding of KM curve where the p value was mentioned were found in 71.4 percent of the studies of which 46.4 percent were highly significant with values less than 0.001 to 0.0001 and 25 percent were significant with values close to 0.05, whereas 14.3 percent were non significant with value greater than 0.05 and the 14.3 percent had not mentioned the significance of the Kaplan Meier's curve. Survival Analysis was done in 20 studies of which nine were highly significant in p value, five were significant for p value, one, was not significant and four studied had not mentioned any p value. Failure time analysis was done in one study, both studies the Kaplan Meier's curve was found to be highly significant. Time to event analysis was done in seven studies, one study was found to be highly significant for p value, two studies were significant for p values, three studies were not significant and four did not mention significance values for p.

Table 3: Showing distribution of significance of age and KM curve.

Variable		KM Significance		Total
		0.0	1.0	
Age	0.0	1	8	9
Significance	1.0	8	11	19
Total		9	19	28

Fisher's Exact Test p=0.195 was not significant

DISCUSSION

This is the first systematic review to date related to interpreting Kaplan Meier's survival curve in patients with COVID-19. Only 28 studies were eligible for inclusion for the time period March 1, 2020 to September 11, 2020, most of which were conducted in China. Nineteen of the studies Kaplan Meier's curves were significant for the study of concern of which thirteen showed highly significant p values <0.001, seven studies showed significant values and four were nonsignificant. Four studies did not mention p values. The survival analysis, which looked into the mortality profile of the patients, the failure time analysis showed the effects of failure of survival and the time to event showed the effects of drugs on morbidity and mortality. Age significance in the study need not necessarily imply that Kaplan Meier's curve would be rendered significant as it seems to be independent of the age variable.[6]

Survival analysis of the patients in Baycan et al case control study, 22 died in the hospital. The parameters affecting mortality were evaluated by including LV-GLS and RV-LS in the two models separately using logistic

regression analysis with univariate and multivariate analysis. KM curve was single and p value, not significant in this study, contrarily significant association between worse LV function and GLS values and mortality was observed in a similar study.[7,8] Wittel et al studied the cumulative survival with multiple KM curves during follow-up according to risk groups of PROFUND and CURB-65 indices, in which significant differences (p=0.01) in outcome trajectories according to risk strata, were obtained. A significant proportion of admitted COVID-19 patients progress to respiratory failure within 24 hours of admission. These events are accurately predicted using bedside respiratory examination findings within a simple scoring system.[9,10] Cao et al's Kaplan-Meier plot with double curve for survial past hospital admission stratified by hs-cTnI levels. Patients were considered to be right-censored if they were discharged alive from hospital or were still in hospital at the time of data freeze, these findings suggest that high levels of hs-cTnT may serve as an early marker of subclinical alterations in diastolic function that may lead to a predisposition to heart failure.[11,12] Cheng et al, Multiple KM survival estimates according to blood urea nitrogen (BUN) and D-dimer levels can be used to estimate the severity of COVID-19.[13,14] Francone et al's Kaplan-Meier analysis, the risk of death significantly increased with the increase of CT score value using an estimated cut-off of ≥18.[15] Gao et al showed Kaplan-Meier plots on the cumulative survival rate of COVID-19 patients who were stratified into two groups according to plasma NT-proBNP cut off point at baseline. Kaplan Meier curve was highly significant (p<0.001), NT-proBNP level appears to be a good predictor of ICU admission and 30-day mortality among inpatients with CAP, with a predictive value for mortality comparable to that of the PSI and better than that of the CURB-65 score.[16,17] Jang et al cumulative risk of 28-day mortality according to the NEWS stratification showed survival time.[18] Liu et al to explore whether a specific antiviralagent was independently associated with prolonged survival.[19] Desir et al demonstrating no significant difference in hospital length of stay between patients with (N 5 163) and without (N 5 1135) asthma, despite a substantial prevalence of asthma in our COVID-19 cohort, asthma was not associated with an increased risk of hospitalization. Similarly, the use of inhaled corticosteroids with or without systemic corticosteroids was not associated with COVID-19 related hospitalization.[20,21]

Shang et al's Kaplan-Meier survival curve showed that the insulin-required diabetic patients had shorter overall survival time (p<0.01). The mortality rate in patients with severe covid-19 with diabetes is considerable. Diabetes may lead to an increase in the risk of death.[22,23] Uribarri et al Kaplan-Meier survival landmark analysis according to the glomerular filtration rate was found to be highly significant p<0.001. Close to 30% of them had evidence of kidney disease on admission, with elevated serum creatinine, and this was associated with greater in-hospital mortality.[24] Wan et al found significant difference in survival rate between the mild and severe groups. Lymphocyte subsets play an important role in cellular immune regulation with each cell restricting and regulating one another. $CD4^+$ T and $CD8^+$ T in the severe group had greater reductions than those in the mild group. This suggested that T lymphocytes provide an important defence against COVID-19.[25,26] Wang et al analysed the correlation between high-density lipoprotein cholesterol (HDL-C) and the severity of COVID-19. Patients with low HDL-C showed a higher risk of developing severe events compared with those with high HDL-C. Development of hypolipidemia begins in patients with mild symptoms. It progressively becomes worse in an association with the disease severity.[27,28] Wu et al's studied survival curves developed using the Kaplan-Meier method with log-rank test. Time to events (ARDS or death) was defined as the time from hospital admission to events. The administration of methylprednisolone appears to have reduced the risk of death in patients with ARDS (HR, 0.38; 95% CI, 0.20-0.72; p=0.003), Acute lung injury and acute respiratory distress syndrome are partly caused by host immune responses. Corticosteroids suppress lung inflammation but also inhibit immune responses and pathogen clearance. In SARS-CoV infection, as with influenza, systemic inflammation is associated with adverse outcomes.[29,30] Zhang et al studied the adjusted survival curve of severe events showed that cancer patients who underwent anti-tumour treatment in the past 14 days or had patchy consolidation in CT on admission had significantly higher severe events. Patients with cancer might have a higher risk of COVID-19 than individuals without cancer.[31,32] Zhang showed association between statin usage and 28-day all cause death was calculated with an adjusted HR of 0.58 (95%CI, 0.43-0.80; p=0.001) compared to non-statin group.[33] Rossi et al studied survival curve, for tocilizumab and control group, showed a significantly greater survival rate of tocilizumab patients as compared to controls.[34,35]

Failure time analysis of patients in a study by Davido et al found unfavorable outcome according to biological parameters (Kaplan-Meier curves p=0.009). Patients who benefited from AZI ±HCQ with CRP ≥100 mg/l were less likely to have an unfavourable outcome compared with patients with no treatment.[36] Hydroxychloroquine administrations was not associated with either a greatly lowered or an increased risk of the composite end point of intubation or death.[37,38]

Time to event analysis was done in seven studies, Choi et al, Kaplan-Meier survival double curve analysis of progression-free survival: according to lopinavir/ritonavir treatment for patients with COVID-19 before and after propensity-score matching. A study by Cao et al found that lopinavir-ritonavir treatment did not significantly accelerate clinical improvement, reduce mortality, or diminish throat viral RNA detectability in patients with serious Covid-19. hazard ratio for clinical improvement, 1.31; 95% confidence interval (CI 0.95 to 1.80;

p=0.09).[39,40] Campiola et al KM curves were two type single curve for Patients had a median time from positive to negative PCR of 17 days and multiple curves representing symptoms. Zhou reported on the persistence of viral RNA for a median of 20 days after symptom onset The median time from symptom onset to CVS was 23 (IQR 12) days, and this did not differ significantly when stratified by symptom.[41,42] Green et al's approach was used to estimate the conversion rate by day of testing with the following assumptions with Kaplan-Meier estimate of conversion rate from initially negative SARS-CoV-2 status on day 1 to a subsequent positive result. Conversion from first-day negative to positive results increased linearly with each day of testing, reaching 25% probability in 20 days. The results demonstrated that the median duration between the onset of symptoms to nucleic acid conversion was 24 days (IQR, 18-31) and that the longest duration was 42 days after the onset of symptoms.[43,44] Hou et al compared the Kaplan-Meier curve of CRISPR-COVID positive rate by CRISPR and PCR. The CRISPR assay functionality is being applied for detection of DNA or RNA using nucleic acid pre-amplification combined with CRISPR-Cas enzymology for specific recognition of sequences.[45] Lagier et al estimates show that the proportion of patients with positive PCR 10 days after inclusion was significantly lower among patients treated with HCQ-AZ. From the efficacy perspective, HCQ (plus azithromycin) may decrease the viral shedding and contagiousness of COVID-19, reduce admission.[46,47] Meng et al's study displays the Kaplan-Meier curve for the length of hospital stay for discharged patients, The median hospital length of stay was 19 days [interquartile range (IQR): 14-23, Range: 3-41].[48-50] Yang.et al studies to identify the factors that affect COVID-19 progression. Older age increased CRP and decreased lymphocyte count resulted in potential risk factors for COVID-19 progression. This may be helpful in identifying patients whose condition worsens at an early stage.[51,52] In Table 3 the Fisher exact test is a nonparametric test for categorical data shows the significance levels of age and KM curve in the selected studies. Fisher's non-parametric test was 0.195 which was found to be not significant.

CONCLUSION

Kaplan Meier's graph has been used singularly, in multiples giving the significance by log rank or p value and cumulatively, thus giving visual assessment which enhances the interpretation of results for survival analysis, failure to time and time to event plots, in a snap shot. Age significance in the study need not necessarily imply that Kaplan Meier's curve would be rendered significant as it seems to be independent of the age variable. It is not only used in RCT study designs but a range of observational and retrospective studies to compare time to event progression.

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