Comparison of Ventilator-free Days at 14 and 28 days as a Clinical Trial Outcome in Low- and Middle-income Countries

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Abstract

Aims and objectives: Reporting ventilator-free days (VFDs) with time frame of 28 days is a popular composite outcome measure (COM) in trials. However, early deaths and shorter pediatric intensive care unit (PICU) stay predominate in low- and middle-income countries (LMICs). A shorter time frame may reduce sample size required. We planned to compute sample size requirements for different effect sizes from datasets of previously conducted prospective studies for 28-day and 14-day time frames (VFD_{28} vs VFD_{14}) to examine the hypothesis.

Materials and methods: The VFD_{28} and VFD_{14} were defined. Datasets of five prospective studies from PICU of our hospital were analyzed to estimate sample sizes for target reductions of 1–9 days in VFDs and other COMs for the two time frames. Reconfirmation of results was done with datasets of two other studies from PICUs of two geographical extremes of the country.

Results: Time-to-event occurred within 14 days in majority of patients. Sample size required for VFD_{14} is about one-fifth to one-sixth of what is required for VFD_{28} for target reductions of 1–9 days for all the enrolled studies. The same was true for other COMs as well. The hypothesis was supported by datasets of two other studies used for reconfirmation.

Conclusion: Choice of time frame for assessing VFDs and other COMs in clinical trials should be guided by the clinical context. A shorter time frame may be rewarding in terms of smaller sample size in the prevalent clinical setting of LMICs. Further confirmation with more datasets and prospective studies is desirable.

Keywords: Children, Clinical trials, Composite outcome measures, Intensive care, Low- and middle-income countries, Ventilator-free days.

Indian Journal of Critical Care Medicine (2020): 10.5005/jp-journals-10071-23568

Introduction

Mortality in critically ill patients is multifactorial, and reduction with anyone intervention is unlikely in the current era.[1] Mortality difference as endpoint would need large sample, which may not only be expensive and difficult to manage but it is also unethical to enroll large number of patients if smaller sample can give similar conclusion.[1–3] Thus, clinical researchers resorted to composite outcome measures (COMs) like ventilator-free days (VFDs), which summarizes both ventilator days and mortality. Improvement in VFDs and other similar COMs, whose parallelism with mortality has been proven statistically, may not only increase cost-effectiveness of an intervention but also improve the survival.[1,2,4] Ventilator-free day is used as primary endpoint in clinical trials[3,5,6] despite its limitations.[4,5] Other popular COMs are vasoactive-inotrope-free days,[6,7] organ failure-free days (OFFDs),[7] renal replacement-free days,[6] ICU-free days,[8–10] and hospital-free days.[9,11,12]

Deaths among critically ill patients have two peaks—"early" ones (i.e., during 14 days) are due to inadequate resuscitation, while "late" ones (i.e., beyond 3rd week) are due to persistence of existing organ dysfunctions and/or appearance of new ones.[13] Significant reduction in "early" deaths in high-income countries (HICs) due to effective implementation of resuscitative care bundles[2,13] has shifted the focus to "late" deaths, which are affected by high prevalence of comorbidities.[2,13–17] Thus, clinical efficacy of interventions is likely to be apparent only over a longer observation period necessitating VFD to be reported in 28 days.[2,4,13,18] However, in low- and middle-income countries (LMICs), critical illnesses are mostly due to acute communicable diseases causing septic shock,[14,19–24] acute respiratory distress syndrome (ARDS),[19,25–28] acute meningoencephalitis,[29] and multi-organ failure in apparently healthy immunocompetent patients without significant comorbidities. Pediatric intensive care units (PICUs) of various LMICs (e.g., Pakistan,[22,23] India,[19,20,24,26,29] Brazil,[25,30] Singapore[28]) report need of shorter (7–14 days) ventilation and/or PICU stay in majority of patients. "Early deaths" in patients from LMICs are attributable to suboptimal acute care facilities, late referral, and poor implementation of time-tested and clinically proven resuscitative bundles.[31]

There is a felt need of appropriate time frames for calculation of VFDs and other COMs according to the time-to-outcome events,[4,32] which is likely to be different in different clinical settings as discussed above. We proposed concept of a shorter time frame (of 14 days) for VFDs and OFFDs in a study in the year 2008[19,33] and reported acute care area-free days (ACAFDs) with time frame of 14 days for

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How to cite this article: Baranwal AK, Kumar MP, Gupta PK. Comparison of Ventilator-free Days at 14 and 28 days as a Clinical Trial Outcome in Low- and Middle-income Countries. Indian J Crit Care Med 2020;24(10):960–966.

Source of support: Nil

Conflict of interest: None

recently.[20] Review of datasets of our previously published studies revealed a considerably lower standard deviation (SD) of the means of VFDs and ACAFDs, respectively, for time frame of 14 days (VFD_{14}) compared to that of 28 days (VFD_{28}).[19,20] As sample size calculation considers SD of the endpoint, we hypothesized that setting a shorter time frame (14 day instead of 28 day) as a COM is likely to reduce the sample size. This *post hoc* analysis was planned to test this hypothesis based on inputs from previously conducted studies.

Materials and Methods

Patients

The study was planned as a *post hoc* analysis. We studied patients enrolled in seven studies,[19,20,27,34–37] out of which four are published.[19,20,27,36] Six of these studies were conducted at Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, while one was conducted at Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pudducherry.[37] Deidentified datasets were obtained by contacting the corresponding authors of the respective studies. We planned to use information from five studies of PGIMER, Chandigarh for evaluation of hypothesis. We then checked if the observed findings were true from datasets of two studies, which we called as reconfirmation cohort: one study from PGIMER, Chandigarh[36] and one from JIPMER, Puducherry.[37] Data for VFDs were available in three studies only, while data for other COMs were available in other studies.

We computed sample size required for interventional studies based on VFD and other COMs with reference to 28 days and 14 days with varying effect size (from 1 free day to 9 free days), and decided to compare the fold change in requirement of sample size. Definition of VFD and other COMs evaluated are detailed in Table 1. The first step was to compute these COMs for the included studies from the available datasets. All data required to calculate the considered COMs were not reported in the included studies. Data for calculating VFDs were present in three studies,[19,27,34] for PICUFDs were present in three studies,[19,34,35] for OFFDs and ACAFDs was present in one study each.[19,20] After computation of

Table 1: Definition of various composite outcome measures in reference to day 28 and day 14 time frames

Outcome name	*Outcome definition*
VFD-28[1] (ventilator-free days in 28 days)	$VFD_{28} = 0$: If patient dies before 28 days of ventilation
	$VFD_{28} = 0$: If patient requires ventilation for >28 days
	$VFD_{28} = (28 - x)$: If patient survives and got weaned from ventilation within 28 days, where "*x*" is the number of days on ventilation
VFD-14[19] (ventilator-free days in 14 days)	$VFD_{14} = 0$: If patient dies before 14 days of ventilation
	$VFD_{14} = 0$: If patient requires ventilation for >14 days
	$VFD_{14} = (14 - x)$: If patient survives and got weaned from ventilation within 14 days, where "*x*" is the number of days on ventilation
PICUFD-28 (pediatric intensive care unit-free days in 28 days)	$PICUFD_{28} = 0$: If patient dies within 28 days of PICU stay
	$PICUFD_{28} = 0$: If patient requires PICU stay for >28 days
	$PICUFD_{28} = (28 - x)$: If patient survives and got discharged from PICU within 28 days, where "*x*" is the number of PICU stay in days
PICUFD-14 (pediatric intensive care unit-free days in 14 days)	$PICUFD_{14} = 0$: If patient dies within 14 days of PICU stay
	$PICUFD_{14} = 0$: If patient requires PICU stay for >14 days
	$PICUFD_{14} = (14–x)$: If patient survives and got discharged from PICU within 14 days, where "*x*" is the number of PICU stay in days
OFFD-28 (organ failure-free days in 28 days)	$OFFD_{28} = 0$: If patient dies within 28 days of developing an organ failure
	$OFFD_{28} = 0$: If patient has an organ failure for >28 days
	$OFFD_{28} = (28–x)$: If patient survives and becomes free from every organ failure within 28 days, where "*x*" is the number of days of organ failure
OFFD-14 (organ failure-free days in 14 days)	$OFFD_{14} = 0$: If patient dies within 28 days of developing an organ failure
	$OFFD_{14} = 0$: If patient has an organ failure for >28 days.
	$OFFD_{14} = (14 - x)$: If patient survives and becomes free from every organ failure within 14 days, where "*x*" is the number of days of organ failure
ACAFD-28 (acute care area free days in 28 days)	$ACAFD_{28} = 0$: If patient dies within 28 days of ACA stay
	$ACAFD_{28} = 0$: If patient requires ACA stay for >28 days.
	$ACAFD_{28} = (28 - x)$: If patient survives and got discharged from ACA within 28 days, where "*x*" is the number of ACA stay in days
ACAFD-14 (acute care area free days in 14 days)	$ACAFD_{14} = 0$: If patient dies within 14 days of ACA stay
	$ACAFD_{14} = 0$: If patient requires ACA stay for >14 days
	$ACAFD_{14} = (14 - x)$: If patient survives and got discharged from ACA within 14 days, where "*x*" is the number of ACA stay in days

COMs, the mean and SD were calculated. In case of observational study,[20] SD was based on the entire study population. There were no difference in the COMs between intervention arms of the interventional studies.[19,27,34,35] Thus, we did not take intervention into consideration and calculated the mean and SD of the entire study population considering them as unity. After computation of mean and SD, the next step was the calculation of sample size for each COM. Approval from ethics committees of respective hospitals had already been obtained for each individual study from which the data were obtained. Hence, a separate ethical approval for the current *post hoc* analysis was deemed not to be required. The analysis was approved by the Departmental Review Board of Department of Pediatrics at PGIMER, Chandigarh.

To justify that the time frame of 14 days is relevant in our clinical setting, we planned to compare if the outcome event (i.e., mortality and freedom from the considered morbidity, e.g., ventilation duration in case of VFDs) occurred in the majority within 14 days or afterward. Hence, we plotted Kaplan Meier curves to evaluate time-to-outcome event (i.e., time-to-death and time-to-extubation in case of VFDs) from datasets of the included studies. The 30-day median survival time (with 95% confidence interval) was computed.

Computation of the Required Sample Size

We assumed that COMs follow normal distribution. For simplicity, we assessed the sample size required for comparison between two independent groups based on COM. We varied the effect size between 1 free day and 9 free days for the COMs. The sample size computation formula for comparing two independent means based on equality assumption, i.e., unpaired *t*-test, is:

$$n = \left[2\left(Z_{\alpha/2} + Z_{\beta}\right)^2 * \mathrm{SD}^2\right] \Big/ d^2$$

(where *Z*, normal distribution; α, type I error; β, type II error; *d*, mean difference ($\mu_1 - \mu_2$) (where μ_1 and μ_2, means of the two groups); SD, pooled standard deviation).

We kept two-sided significance along with type I error at 0.05 and type II error at 0.2 (power 0.8) for all the calculations. The sample size computed was for single group. From this information, sample size required for VFDs and other COMs with time frames of 28 days and 14 days were compared. Statistical analysis was done using R version 3.5.1[38] and its additional packages like were pwr,[39] ggplot2,[40] and pROC.[41]

Results

Characteristics of the studies included for concept evaluation as well as the studies used for reconfirmation and relevant data summary therefrom are shown in Table 2.

Time-to-outcome Event in the Included Studies

Kaplan Meier curves for time-to-outcome event (death or extubation) for three representative studies (Choudhary,[34] Jain,[37] and Yadav et al.[36]) are shown in Figure 1. The 30-day median time to event for death was 11 days (95% CI, 7–14) and 9 days (95% CI, 7–13) in the studies by Jain[37] and Yadav et al.,[36] respectively. The median survival time for the Chaudhary's study[34] could not be calculated as mortality was less than 50%. The 30-day median time to event for extubation was 9 days (95% CI, 7–12), 6 days (95% CI, 5–8), and 7.5 days (95% CI, 6–10) in the studies by Chaudhary,[34] Jain,[37] and Yadav et al.,[36] respectively.

Estimation of Sample Size with VFD14 and VFD28

Utilizing datasets from studies of Baranwal et al.,[19] Lalgudi Ganesan et al.,[27] and Choudhary,[34] the comparative analysis of computed requirement of sample size to prove significance for VFD_{14} and VFD_{28} is shown in Figure 2. The curves for VFD_{14} and VFD_{28} converge with increase in effect size; however, the ratio between them remained approximately same throughout. The estimated sample sizes for target reductions of 1 day, 5 days, and 9 days are shown in Table 3. Sample sizes required for VFD_{28} are 5.99, 5.91, and 6.65 times of that are required for VFD_{14} for target reduction of 1 day based on the dataset from Baranwal et al.,[19] Lalgudi Ganesan et al.,[27] and Choudhary,[34] respectively. Similarly, 5.33, 5.36, 6.11 and 5.0, 4.8, 4.5 times bigger samples are required for VFD_{28} compared to that of VFD_{14} for target reductions of 5 and 9 days, respectively, in these three studies. On an average, 6.19 ± 0.41, 5.60 ± 0.44, and 4.77 ± 0.25 times larger samples are required for VFD_{28} compared to VFD_{14} for target reduction of 1, 5, and 9 days respectively. Similar trends were seen for other COMs (Table 3). Studies used for reconfirmation of the hypothesis also revealed similar results (Tables 2 and 3).

Discussion

In the current *post hoc* analysis of datasets from previously conducted studies at our tertiary care teaching hospital, we demonstrated that death and extubation predominantly occurred within 14 days. By reducing time frame of VFDs to 14 days, required sample size got significantly reduced compared to that of 28 days. The desired difference of VFD was varied between 1 day and 9 days for sample size calculation as mean duration of ventilation among survivors was 8–11 days.[19,27,34] Approximately five and half times less sample is required for the time frame of 14 days compared to that of 28 days. It provided a proof of concept to our hypothesis. Datasets of another study from our hospital and a study from a hospital situated in southern part of India[36,37] further supported it.

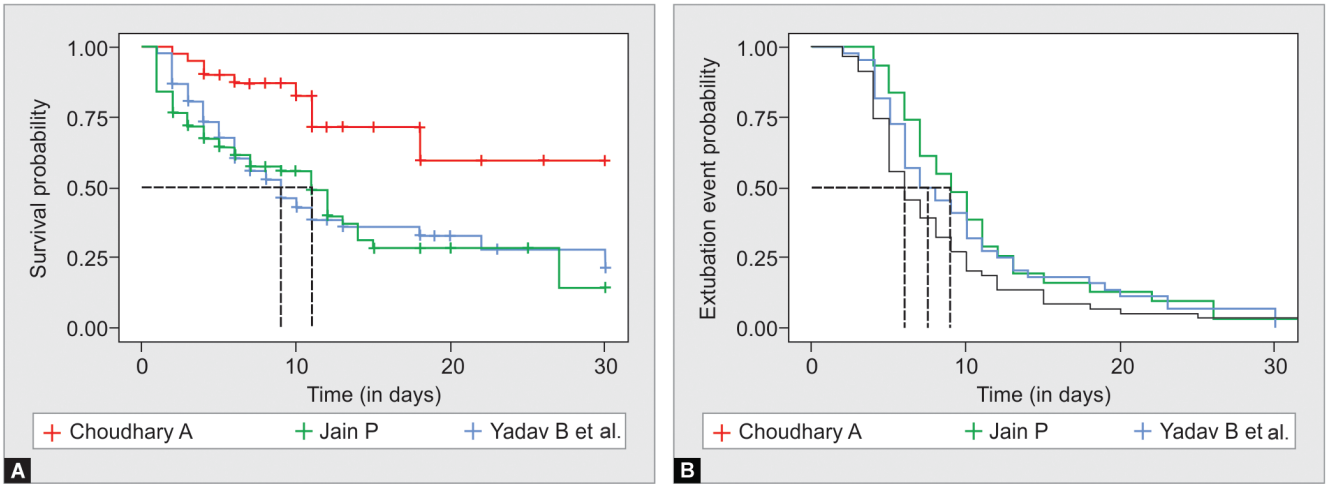
The VFDs and other COMs are widely being used to reduce sample size while capturing clinically meaningful outcomes.[1,2,4,5] Though time frames of 28 days or longer are popular in the studies from HICs, questions are being raised regarding clinical utility of longer observation period if majority of patients experience the outcome event in a shorter time frame.[5,32] Most of children in PICUs of the LMICs are suffering from easily treatable communicable diseases and do not have significant comorbidities compared to those in HICs. Consequently, majority require shorter ventilation and PICU stay as demonstrated in the current analysis. Bodet-Contentin et al.[4] suggest "the time horizon should be established in light of the medical context i.e., when one can reasonably expect that most patients are extubated or dead." Yehya et al. concluded with similar sentiments in their reappraisal of VFDs.[32] A shorter time frame (i.e., 14 days) is likely to help design fully powered trials with smaller samples for shorter observation period, which is likely to impact feasibility and cost of conducting a trial. It may improve generation of quality scientific data from LMICs to arrive at meaningful conclusions with potentially useful interventions.

Earlier studies demonstrated that statistical properties of VFDs depend on choice of time frame (14, 28, 60, or 90 days) and method of hypothesis testing (nonparametric vs parametric test).[1,4] The parametric test (e.g., Student's *t*-test) is likely to reduce weightage for survivals for 14-day time frame compared to 28-day time frame because survivals would have less VFDs in case of the former.[1] Thus, nonparametric test (e.g., Wilcoxon rank-sum test) is advised for the

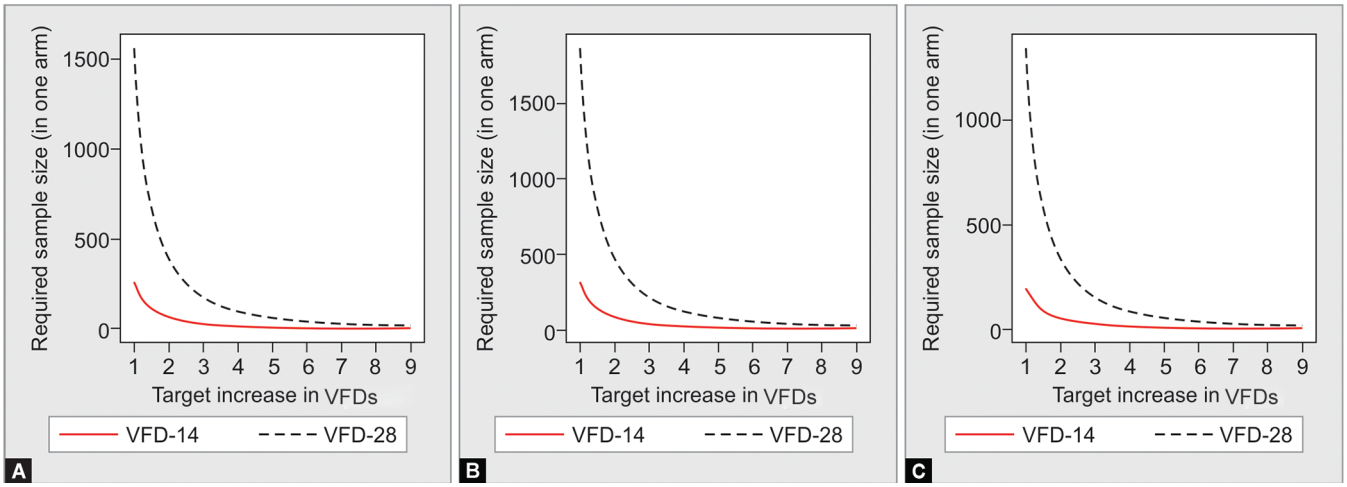
Table 2: Characteristics of the included studies

Studies	*Study design*	*Nature of enrolled patients*	*Intervention if any*	*Sample size*	*Mortality, n (%)*	*VFD_{14} (mean ± SD)*	*VFD_{28} (mean ± SD)*	*SD taken for computing sample size for VFD_{14}*	*SD taken for computing sample size for VFD_{28}*
Baranwal et al.[19]	Interventional study	ARDS	Oral ambroxol vs placebo	66	17 (26)	4.70 ± 4.07	14.36 ± 9.98	4.07	9.98
Lalgudi Ganesan et al.[27]	Interventional study	ARDS	APRV vs standard ventilation	52	21 (40)	4.12 ± 4.47	11.96 ± 10.89	4.47	10.89
Choudhary[34]	Interventional study	ARDS	Lower vs higher hemoglobin threshold for transfusion	40	9 (23)	3.65 ± 3.58	13.23 ± 9.25	3.58	9.25
						$OFFD_{14}$	$OFFD_{28}$		
Baranwal et al.[19]	Interventional study	ARDS	Oral ambroxol vs placebo	66	17 (26)	7.92 ± 5.59	17.76 ± 11.45	5.59	11.45
						$PICUFD_{14}$	$PICUFD_{28}$		
Baranwal et al.[19]	Interventional study	ARDS	Oral ambroxol vs placebo	66	17 (26)	2.23 ± 3.01	11.32 ± 8.46	3.01	8.46
Gupta[35]	Interventional study	Septic shock	Normal saline vs plasmalyte	44	10 (23)	4.61 ± 4.36	14.64 ± 9.64	4.36	9.64
Choudhary[34]	Interventional study	ARDS	Lower vs higher hemoglobin threshold for transfusion	40	9 (23)	2.40 ± 3.22	10.70 ± 9.04	3.22	9.04
						$ACAFD_{14}$	$ACAFD_{28}$		
Ghosh et al.[20]	Observational study	Septic shock	None	42	16 (38)	3.40 ± 4.07	11.81 ± 10.07	4.07	10.07
						VFD_{14}	VFD_{28}		
Jain[37]	Interventional study	Septic shock	EGDT vs standard care	120	61 (51)	3.36 ± 4.22	9.72 ± 10.72	4.22	10.72
Yadav et al.[36]	Observational study	ARDS	None	98	54 (55)	2.49 ± 3.78	8.01 ± 10.10	3.78	10.10
						$PICUFD_{14}$	$PICUFD_{28}$		
Jain[37]	Interventional study	Septic shock	EGDT vs standard care	120	61 (51)	2.36 ± 3.42	8.45 ± 9.78	3.42	9.78

RCT, randomized controlled trial; VFD, ventilation-free days; OFFD, organ failure-free days; PICUFD, pediatric intensive care unit-free days; ACAFD, acute care area-free days; ROC AUC, receiver operating characteristics area under curve; EGDT, early goal-directed therapy; APRV, airway pressure release ventilation



Figs 1A and B: Kaplan Meier curves to show the time to event for deaths (A) and extubations (B) in three recent studies from India (Choudhary,[34] Jain,[37] and Yadav et al.[36] Horizontal lines represent the median time to event. In the study by Choudhary,[34] the median time to death could not be computed (A), as the mortality was <50% during the observation period of 30 days



Figs 2A to C: Comparison of the estimated sample sizes in one arm for various target increments in ventilation-free days (VFD) for time frames of 14 days (VFD_{14}) vs 28 days (VFD_{28}) based on the real dataset from: (A) Baranwal et al.;[19] (B) Lalgudi Ganesan et al.;[27] (C) Choudhary[34]

Table 3: Comparison of calculated sample sizes required in one arm for three target increments (1, 5, and 7 days) in various composite outcome measures for time frames of 14 and 28 days

		Comparison of sample sizes required in one arm for different target increments in the respective composite outcome measures with respect to the two time frames		
	Studies	*1 day's increment*	*5 days' increment*	*9 days' increment*
Studies used for evaluation of concept				
1.	Baranwal et al.[19]			
	VFD_{14}:VFD_{28}	261:1565	12:64	4:20
2.	Lalgudi Ganesan et al.[27]			
	VFD_{14}:VFD_{28}	315:1863	14:75	5:24
3.	Choudhary[34]			
	VFD_{14}:VFD_{28}	202:1344	9:55	4:18
4.	Baranwal et al.[19]			
	$OFFD_{14}$:$OFFD_{28}$	492:2059	21:83	7:26
5.	Baranwal et al.[19]			
	$PICUFD_{14}$:$PICUFD_{28}$	143:1125	7:46	3:15
6.	Gupta[35]			
	$PICUFD_{14}$:$PICUFD_{28}$	299:1460	13:59	5:19
7.	Choudhary[34]			
	$PICUFD_{14}$:$PICUFD_{28}$	164:1284	8:52	3:17
8.	Ghosh et al.[20]			
	$ACAFD_{14}$:$ACAFD_{28}$	261:1593	11:65	4:21
Studies used for reconfirmation of concept				
9.	Yadav et al.[36]			
	VFD_{14}:VFD_{28}	225:1602	10:65	4:21
10.	Jain[37]			
	VFD_{14}:VFD_{28}	281:1805	12:73	5:23
11.	Jain[36]			
	$PICUFD_{14}$:$PICUFD_{28}$	185:1502	8:61	4:20

VFD, ventilation-free days; OFFD, organ failure-free days; PICUFD, pediatric intensive care unit-free days; ACAFD, acute care area-free days

extremely skewed VFD distribution as it will be independent of the length of time frame.[1,4] However, reducing time frame from 28 to 14 days is likely to reduce skewness of VFDs and increase applicability of the parametric test.[32] Further, the *t*-test is considered adequate for sufficiently large sample size (>30 patients).[4] All the included studies for the current analysis have reasonable sample size. Though Gray's test and Fine and Gray regression test are suggested to be preferred over Wilcoxon rank-sum test or Student's *t*-test for

assessment of competing events (mortality and ventilator days) by comparing the cumulative incidence functions,[4,32] the former ones are not popular even in recently conducted clinical trials[42–44] and *post hoc* analysis.[45] Moreover, Student's *t*-test performed well while evaluating power of study for different outcomes compared to Grey's test and Fine and Gray regression test.[32]

Median time-to-outcome event for death and extubation in our PICUs is demonstrably less than 14 days; however, a comparative analysis of datasets from HICs and other LMICs would have improved interpretation. Considering small and single-center studies arbitrarily without a predefined protocol is a limitation. Potential bias toward a specific clinical setting cannot be ruled out as all the datasets included are from one country, and all except one are from a single hospital. However, the statistical approach and calculated sample sizes therefrom are strong enough to provide a scientifically meaningful proof of concept. Validation of the concept from more datasets in a more scientific manner is likely to improve external validity.

Conclusion

The *post hoc* analysis provided a proof of concept that choice of the time frame for assessing VFDs and other COMs should be guided by the clinical context and the time-to-outcome event. A shorter time frame of 14 days is likely to require much smaller sample size compared to the time frame of 28 days in LMICs especially among pediatric patients. However, it needs to be validated with more datasets and prospective studies.

Acknowledgments

We would like to thank Prof Jayashree Muralidharan, Dr Arun Bansal, Dr Shalu Gupta, Dr Abhijit Choudhary, and Dr Puneet Jain to provide real datasets of their studies.

Role of Contributors

Arun K Baranwal conceived the idea of usefulness of shorter time horizon for composite endpoints from the dataset of his studies, conceptualized the same, prepared the final draft of the manuscript, and will act as guarantor. Arun K Baranwal and Praveen Kumar-M did literature search and statistical analysis. Praveen Kumar-M prepared the first draft of the manuscript. Pramod K Gupta critically reviewed the statistical analysis and manuscript and suggested valuable modifications.

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