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Original Article

Clinical recommendations from an observational study on MERS: glucocorticoids was benefit in treating SARS patients

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Abstract: Objectives: In order to provide the foundation on which recommendations for clinicians in using GC in treating MERS were developed, the accurate effects of different daily and accumulated doses of GC based on the largest SARS database in mainland China were examined. Methods: Survival analysis with different statistical models (including Cox's proportional hazard regression model) was used to examine the effects of GC usage. Results: Usage of glucocorticoids in severe cases could prolong the survival time of clinical cases significantly (P=0.00). In non-severe cases the average daily dose >160 mg was significantly harmful and accumulated dose between 3000 mg and 6000 mg was significantly beneficial. In severe cases, different ranges of the starting dose, the mean dose of first 3 days, the average daily dose, and the daily maximum dose dropped death risk significantly; the accumulated dose of 1000-3000 mg, 3000-6000 mg, and >6000 mg prolonged the survival time of clinical cases significantly and showed dose response relationship. Conclusions: GC therapy was beneficial for severe SARS patients. Clinicians should take patients' conditions, clinical stage, daily dose, accumulated dose, and duration of treatment into consideration carefully when judging how to use GC in MERS treatment.

Keywords: SARS, GC treatment, MERS, daily dose, accumulated dose

Introduction

Middle East respiratory syndrome coronavirus (MERS-CoV), a novel human coronavirus that was isolated from a 60-year-old Saudi Arabian patient In June 2012, is now considered a threat to global public health. Although two years have passed since the initial description of MERS, the case fatality rate of MERS still stays at a high level, from 27% to 50% [1-6]. One of the key reasons of the high case fatality lies that virus infections follow an unusually aggressive clinical course with rapid deterioration. Most cases frequently presented with fever and cough, but then some of them were more likely to develop lower respiratory tract symptoms or rapidly progress to severe pneumonia. Meanwhile, severe cases were often complicated with ARDS [6-11]. To date, no efficient treatment strategies in treating MERS and its related acute lung injury (ALI) and ARDS are available [3-5, 10-15].

Glucocorticoids (GC) therapy is traditional and effective in treating ALI and ARDS [16-18] and it was also used in treating MERS. Jaffar et al described a varied usage of methylprednisolone and prednisolone combined with rabavirin and interferon in five MERS patients, but all patients died 32-52 days after admission, which led to no resolution in GC therapy [19]. Clinicians need more evidence in GC administration for MERS treatment to improve the survival rate.

Partly because the structural comparison between MERS-CoV and SARS-CoV RBDs shows that their core subdomains are homologous and similar in structure [4], the current knowledge of therapeutic options for MERS-CoV is based on the experience from SARS-CoV and in vitro studies [6, 12]. Treatment with Ribavarin and Interferon α-2b has been suggested as a potential therapy for MERS-CoV [15, 20].

China was the most heavily stricken country in SARS outbreak. On July 31, 2003, SARS was described in 29 countries involving 8098 individuals and caused774 deaths [21, 22]. There were 5327 clinically diagnosed cases and 349 deaths in the SARS outbreak in Mainland China. This study was to examine the accurate effects of different daily and accumulated doses of GC, and try to illustrate their effects and get the most suitable therapeutic regimen in both severe and non-severe cases based on the largest SARS database in Mainland China. Survival curves, univariate, adjusted, and stratified Cox's proportional hazard regression models were used to maximize comparability with randomized control trials, although it was an observational study. This study aimed to target a better understanding of GC administration and its clinical benefits to provide evidence on which recommendations to clinicians in curing MERS were made.

Materials and methods

Data resource

The Chinese SARS Clinical Database collected 5,327 clinically diagnosed SARS cases including 349 deaths all over China. Data entered into database as per the source data from medical records after SARS outbreak and were quality-controlled by trained medical staff. Gender, age, occupation, smoking, alcohol, symptom and vital signs (temperature and blood pressure etc.) on admission, treatment (administration of GC etc.), mechanical ventilation, severity of disease, complications (MODS, disseminated TB, DM, infection, DIC etc.), primary diseases (COPD, asthma, hypertension, Cardiovascular and cerebrovascular diseases, cancer, renal failure/chronic renal disease etc.) etc. of patients were collected into the database. Data of GC treatment section, which had 5327 observations, 118 variables and 157730 records, were analyzed.

Selection criteria

Because GC can only have clinical effectiveness at least 48 hrs after administration, those cases who died within 48 hours after admission or died within 48 hours after first dose of GC were excluded from analysis.

Criteria for clinically diagnosed SARS cases

The CDC criteria for clinically diagnosed SARS were applied [23]. Case definitions were as follows: 1) fever (temperature >38°C); 2) chest radiograph (chest X-ray and/or chest CT) showed evidence of consolidation with or without respiratory symptoms such as cough or shortness of breath; 3) history of exposure to an index case suspected of having SARS or direct contact with a person who fell ill following exposure to the index case.

Criteria for severe cases

According to criteria of severe SARS cases by Health Ministry of China, a severe case was defined from 4 items: 1) breathing of more than 30/min; 2) oxygen partial pressure of more than 70 mmHg; 3) blood oxygen saturation of less than 93%; 4) sternum score of greater than or equal to 2 points. In this study, a case was deemed severe if he/she had any of the 4 conditions above.

Definition of GC

Data collected in the database were from all over China where doctors from different hospitals might use different GCs in treatment of patients. To evaluate the effect of GC accurately in terms of the dose-response relationship, GC transformation was performed as: 4 mg methylprednisolone (MP) =0.75 mg dexamethasone =20 mg hydrocortisone. MP dosage was adopted as standard GC dosage in following analysis, i.e. 1 mg GC equals to 1 mg MP.

Five different measurement of GC were observed in this study: 1) use or not, 2) starting dose, 3) average daily dose of first three days, 4) daily maximum dose, and 5) accumulated dose. Starting dose was categorized into four levels: none, 0-80 mg/d, -160 mg/d, and >160

Table 1. Univariate analysis of survival time in SARS patients

Variables	Chi-square values	*P* values
Gender (female vs. male)	12.57	0.00
Age (7 groups)	630.99	0.00
GC (use vs. not)	8.13	0.00
GC starting dose (4 groups)	22.46	0.00
Mean GC dose of first 3 days (4 groups)	22.37	0.00
Average daily dose (3 groups)	407.43	0.00
Maximum GC dose (4 groups)	58.65	0.00
Accumulated GC dose (5 groups)	21.29	0.00
Severity of the case (severe cases vs. not)	267.10	0.00
Mechanical ventilation (use vs. not)	571.47	0.00
MODS (yes vs. not)	1046.80	0.00
Disseminated TB (yes vs. not)	2.63	0.10
DM (yes vs. not)	64.99	0.00
Infection (yes vs. not)	100.54	0.00
DIC (yes vs. not)	93.95	0.00
Cardiovascular and cerebrovascular diseases (yes vs. not)	89.74	0.00
Hypertension (yes vs. not)	159.68	0.00
COPD/asthma (yes vs. not)	2.92	0.09
Renal failure/chronic renal disease (yes vs. not)	27.09	0.00
Cancer (yes vs. not)	25.05	0.00

Notes: age groups: 1: <15; 2: -25; 3: -35; 4: -45; 5: -55; 6: -65; 7: >65; Starting dose: none, 0-80 mg/d, -160 mg/d, and >160 mg/d; mean dose of GC in first 3 days: none, 0-80 mg/d, -160 mg/d, and >160 mg/d; average daily dose: none, 80 mg/d, and >160 mg/d; daily maximum GC dose: none, 0-80 mg/d, -160 mg/d, and >160 mg/d; accumulated GC dose: none, 0-1000 mg, -3000 mg, -6000 mg, and >6000 mg.

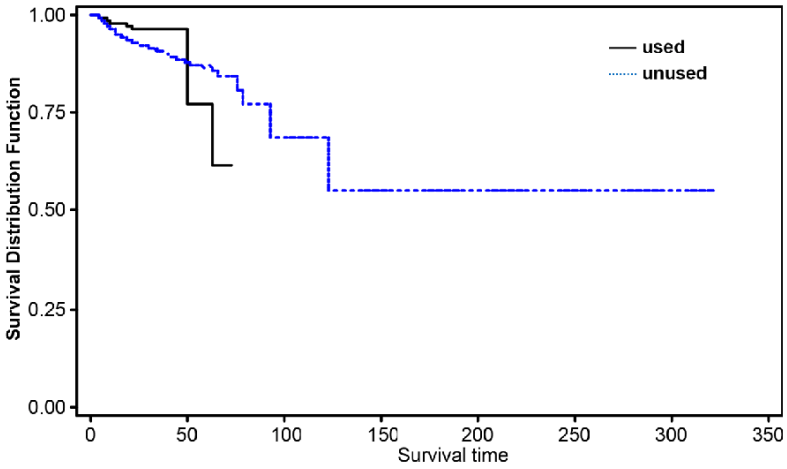

Figure 1. Survival curses on GC used and not used in SARS patients.

mg/d; mean dose of first 3 days was categorized into four levels: none, 0-80 mg/d, -160 mg/d, and >160 mg/d; average daily dose was categorized into three levels: none, 80 mg/d and >160 mg/d; daily maximum dose was categorized into four levels: none, 0-80 mg/d, -160 mg/d, and >160 mg/d; accumulated dose was categorized into five levels: none, 0-1000 mg, -3000 mg, -6000 mg, and >6000 mg.

Definitions of clinical outcomes

Survival time was selected as response variable. Survival time was defined as days from admission till death or discharge.

Data analysis

Univariate Cox's proportional hazard regression (single independent variable was included in the model) was used for selection of variables to be included in final multivariate Cox regression model. Log-Rank test was used to compare the differences. P<0.05 was considered

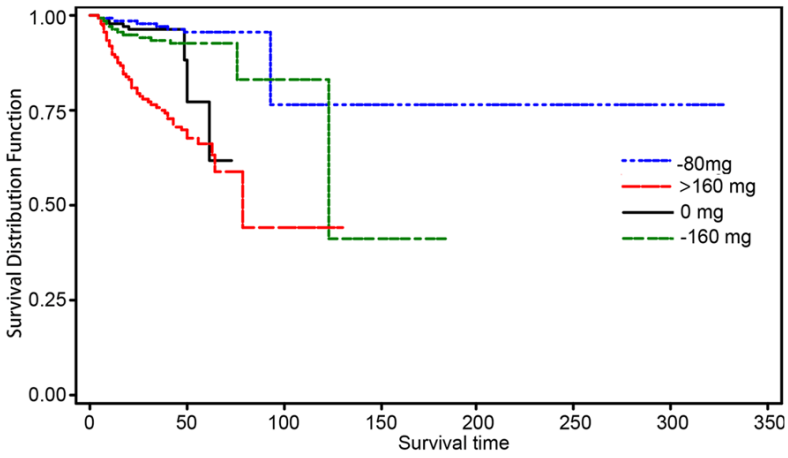

Figure 2. Survival curses on average daily GC doses in SARS patients.

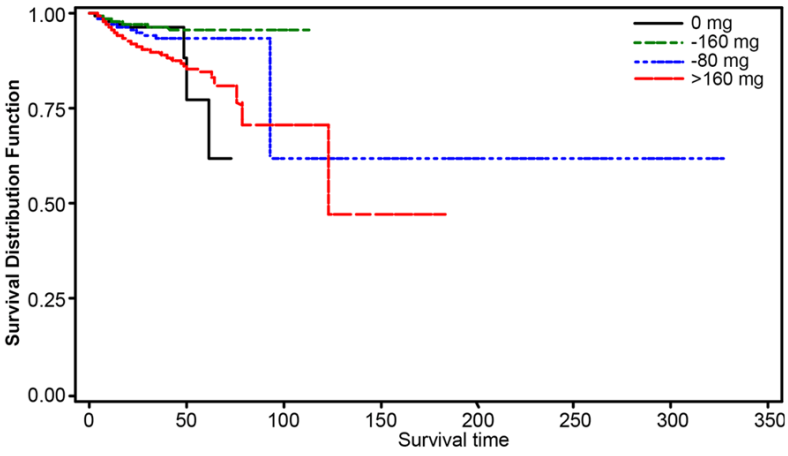

Figure 3. Survival curses on daily maximum GC doses in SARS patients.

statistically significant. Survival curves were plotted for all six variables mentioned above. Multivariate Cox's proportional hazard regression model were then used to evaluate association of CG treatment and survival time after adjustment for gender (male, female), age (<15, -25, -35, -45, -55, -65, >65), occupation, mechanical ventilation, severity of cases, complications and primary diseases, such as COPD, asthma, hypertension, CVD, MODS, DM, infection, cancer and DIC. Finally, stratified analysis was conducted for severe cases and non-severe cases to estimate the associations between CG treatment and outcomes of SARS patients, with the same multivariate Cox regression model used above. The very first level of each variable was used as a reference for calculating the hazard ratios (HRs) and 95% confidence intervals (95% CIs). All statistical analyses were performed by using Statistical Analysis System, version 9.2 (SAS Institute, Inc., Cary, North Carolina).

Ethics statement

This study was approved by the Ethics Committee of the Fourth Military Medical University. All data analyzed in this study were anonymized. All patient records were anonymized and de-identified prior to analysis.

Results

Univariate Cox regression

By univariate Cox regression model, survival time was observed associated with gender, age, starting doses, mean doses in first three days, average daily dose, daily maximum doses, accumulated doses, mechanical ventilation, severity of the case, complications (MODS, DM, infection, DIC etc.), and primary diseases (hypertension, Cardiovascular and cerebrovascular diseases, cancer, renal failure/chronic renal disease etc.), respectively (**Table 1**).

Non-parametric survival analysis

Kaplan-Meier survival curves was plotted for variables including CG administration (used or not), starting doses, mean doses in first three days, average daily doses, daily maximum doses, and accumulated doses, which showed significant differences of survival functions between levels of the factors above and crossing of survival curves existed among some of the levels of factors (**Figures 1-3**).

The survival rate of patients who did not use GC was higher than that of patients who used GC before 50 days of admission, while after 50 days of admission survival rate of patients who

Table 2. Multivariate hazard ratios of CG usages for SARS patients survival (N=5327)

Variables	Groups	Chi-square value	*P* value	HR	95% CI
CG usage starting dose	Used vs. not	4.54	0.03	0.19	0.04-0.88
	0-80 vs. none	1.17	0.28	0.43	0.10-1.97
	-160 vs. none	0.00	0.98	0.00	0.00
	>160 vs. none	0.00	0.98	0.00	0.00
Mean dose in first 3 days	0-80 vs. none	1.28	0.26	0.29	0.03-2.51
	-160 vs. none	0.00	0.98	0.00	0.00
	>160 vs. none	0.00	0.98	0.00	0.00
Average daily dose	0-80 vs. none	20.71	0.01	0.37	0.24-0.56
	-160 vs. none	6.97	0.01	0.57	0.37-0.86
	>160 vs. none	0.82	0.36	1.21	0.80-1.81
Daily maximum dose	0-80 vs. none	0.16	0.69	0.73	0.16-3.40
	-160 vs. none	0.00	0.97	0.00	0.00-0.00
	>160 vs. none	0.00	0.97	0.00	0.00-0.00
Accumulated dose	0-1000 vs. none	0.93	0.34	0.46	0.09-2.24
	-3000 vs. none	0.00	0.97	0.00	0.00
	-6000 vs. none	0.00	0.98	0.00	0.00
	>6000 vs. none	0.00	0.10	0.00	0.00

Note: Adjusted by: gender, age, occupation, mechanical ventilation, severity of the case, complications (MODS, DM, infection, DIC etc.), and primary diseases (hypertension, Cardiovascular and cerebrovascular diseases, cancer, renal failure/chronic renal disease etc.).

did not use GC was even lower than that of patients using GC (**Figure 1**). Survival curves of starting doses, mean doses in first three days, and accumulated doses showed the same trends with **Figure 1** in group of 0 mg compared with other levels of each variable, respectively. In survival curve for average daily dose, survival time of level ≥160 mg/d was the lowest among all levels (**Figure 2**), while that of level 80-160 mg/d was the highest (accessing 100%) among all levels of daily maximum doses (**Figure 3**).

Multivariate Cox regression analysis

With adjustment for gender, age, occupation, mechanical ventilation, severity of cases, complications (MODS, DM, infection, DIC etc.), and primary diseases (hypertension, Cardiovascular and cerebrovascular diseases, cancer, renal failure/chronic renal disease etc.), multivariate Cox's proportional hazard regression showed that usage of GC prolonged survival period of clinical cases significantly (P=0.03) and death risk dropped by 63% (HR: 0.37, 95% CI: 0.24-0.56) and 43% (HR: 0.57, 95% CI: 0.37-0.86) for average daily doses of 0-80 mg/d and 80-160 mg/d, respectively. Starting doses, mean doses in first three days, daily maximum doses, and accumulated doses did not show significant differences among different levels (**Table 2**).

Subgroup analysis

Stratified adjusted multivariate Cox's proportional hazard regression model was used for subgroups of severe cases and non-severe cases. The results showed that usage of GC in severe cases could prolong the survival time significantly (P=0.00), while it was not the case in non-severe cases (P=0.58).

In non-severe cases, patients with accumulated dose between 3000mg and 6000mg had longer survival time (P=0.01), while patients with average daily dose >160 mg had a higher death risk of 1.42 fold (P=0.02); in severe cases, patients with starting dose of -160 mg or >160 mg had longer survival time (P=0.00); For patients with average dose of first 3 days >80 mg (P=0.00) or >160 mg (P=0.00), the death risk dropped by 50-51%; For patients with average daily dose of -160 mg (P=0.00) or >160 mg (P=0.01), the death risk dropped by 47-72%; For patients with daily maximum dose of -160 mg (P=0.00) or >160 mg (P=0.01), the death risk dropped by 45-60%; For patients with accumulated dose of -3000 mg, -6000

Table 3. Stratified multivariate hazard ratios of CG usages for SARS patients survival in severe cases and non-severe cases (N=5327)

Variables	Groups	Non-severe cases				Severe cases			
		Chi-square value	*P* value	HR	95% CL	Chi-square value	*P* value	HR	95% CL
CG usage starting dose	Used vs. not	0.30	0.58	0.84	0.44-1.59	8.29	0.00	0.53	0.35-0.82
	0-80 vs. none	0.03	0.85	0.94	0.46-1.92	2.02	0.16	0.72	0.45-1.13
	-160 vs. none	2.17	0.14	0.57	0.27-1.21	10.44	0.00	0.46	0.28-0.73
	>160 vs. none	0.01	0.92	0.96	0.48-1.94	10.53	0.00	0.46	0.29-0.74
Mean dose in first 3 days	0-80 vs. none	0.18	0.67	0.86	0.42-1.75	3.59	0.06	0.63	0.40-1.02
	-160 vs. none	0.83	0.36	0.71	0.34-1.49	9.05	0.00	0.49	0.30-0.78
	>160 vs. none	0.05	0.82	0.92	0.45-1.87	8.50	0.00	0.50	0.32-0.80
Average daily dose	0-80 vs. none	1.00	0.07	0.51	0.24-1.07	21.98	0.00	0.28	0.16-0.48
	-160 vs. none	0.62	0.43	0.73	0.34-1.59	6.16	0.01	0.53	0.32-0.88
	>160 vs. none	5.66	0.02	2.42	1.17-5.01	0.17	0.68	1.11	0.69-1.78
Daily maximum dose	0-80 vs. none	0.49	0.48	1.34	0.59-3.02	0.97	0.32	0.73	0.39-1.37
	-160 vs. none	2.21	0.14	0.53	0.23-1.22	9.34	0.00	0.40	0.23-0.72
	>160 vs. none	0.30	0.58	0.82	0.41-1.65	6.95	0.01	0.55	0.35-0.86
Accumulated dose	0-1000 vs. none	0.90	0.34	1.37	0.71-2.65	0.17	0.68	0.91	0.58-1.42
	-3000 vs. none	3.08	0.08	0.51	0.25-1.08	9.98	0.00	0.48	0.30-0.75
	-6000 vs. none	6.08	0.01	0.33	0.14-0.80	19.06	0.00	0.33	0.20-0.54
	>6000 vs. none	1.69	0.19	0.54	0.21-1.37	29.31	0.00	0.22	0.13-0.38

Note: Adjusted by: gender, age, occupation, mechanical ventilation, severity of the case, complications (MODS, DM, infection, DIC etc.), and primary diseases (hypertension, Cardiovascular and cerebrovascular diseases, cancer, renal failure/chronic renal disease etc.

mg, and >6000 mg had prolonged survival time in clinical cases and it showed dose response relationship with HRs of 0.48, 0.33, and 0.22, respectively (**Table 3**).

Discussion

In this study, effects of GC administration in treating SARS cases were observed based on the biggest database, which included all consecutive SARS patients from Mainland China. The SARS database used in this study was reliable with all possible measures, assuring data quality and validity. Different statistical models of survival analysis were used with or without adjustment for confounding factors to assure reliability of the results. Subgroup analyses for severe cases and non-severe cases were also performed to explore effects of GC treatment associated with disease severity. Though there might be bias in results of this observational study, certain recommendations can be made for MERS treatment.

This study demonstrated that the usage of GC in treating ALI and ARDS prolonged the survival time of the patients significantly (P=0.03) and decreased the risk of death by 80%. In non-severe cases, an average daily dose of >160 mg was shown harmful to patients. In severe cases, -160 mg/d and >160 mg/d at the beginning, -160 mg/d and >160 mg/d in the first three days, -80 mg/d and -160 mg/d average daily doses, -160 mg and >160 mg daily maximum doses, and -3000 mg, -6000 mg, and >6000 mg accumulated GC doses were shown beneficial to patients.

GC is a traditional therapy in treating common ALI and ARDS [16-18] and it still plays an important role in SARS and MERS related ALI and ARDS. Based on adjustment for gender, age, occupation, mechanical ventilation, complications and primary diseases, it is proved that administration of GC appeared to be relatively safe and effective in treating SARS (HR 0.19, 95% CI: 0.04-0.88). HR of this study was 0.53 (95% CI: 0.35-0.82) in severe cases which indicated that the death risk of severe cases would drop by 47% (P=0.00) when using GC. Meduri analyzed randomized trials of low dose cartico-sterioids in patients with early or late ARDS and included the trial with pneumonia patients, a RR of death of 0.76 (95% CI: 0.62-0.93) was

obtained [18]. Agarwal combined observational and randomized trials and found an OR (0.57, 95% CI: 0.22-1.53) of death favoring carticosterioids in early ARDS and 0.58 (95% CI: 0.22-1.53) of steroids were initiated more than seven days after the onset of ARDS [18, 24]. Eight controlled studies (n=569) evaluating treatment before day 14 of ARDS showed that GC treatment was associated with a significant reduction in the risk of death (RR 0.68, 95% CI: 0.56-0.81) [16, 25, 26]. The results of the related studies of common ALI and ARDS treatment were consistent with this study. They showed that usage of GC can get the same effect between common and SARS related ALI and ARDS which suggested that clinicians could learn some experience from GC treatment of SARS.

It was proved that starting dose of -160mg, mean dose in first three days of -160 mg, and daily maximum dose of -160 mg decreased more than a half of death risk in severe case according to theirs HRs which were 0.46 (95% CI: 0.28-0.73), 0.63 (95% CI: 0.40-1.02), and 0.40 (95% CI: 0.23-0.72), respectively. Survival function for level of -160 mg/d of daily maximum doses remained 100%. Researchers recommended that prolonged MP at 1 mg/kg/d initially in early ARDS, increasing to 2 mg/kg/d after seven to nine days of no improvement [26, 27]. Their recommendation was very close to results of this study based on multiplying by adults' body weight. It clues that clinicians may try the same GC daily dose in treating MERS related ALI and ARDS in severe cases. This study made further progress based on the database of a larger sample size. Both average dose in first three days of >160 mg (HR: 0.50, 95% CI: 0.32-0.80) and daily maximum dose of >160 mg (HR: 0.55, 95% CI: 0.35-0.86) were beneficial for severe cases. It was suggested that clinicians might try higher GC doses in first three days and maximum dose if MERS patients' condition cannot be controlled well with GC dose above mentioned.

In non-severe cases, HR of >160 mg average daily dose was 2.42 (95% CI: 1.17-5.01); in severe cases, HRs of -80 mg and -160 mg average daily doses were 0.28 (95% CI: 0.16-0.48, P=0.00) and 0.53 (95% CI: 0.32-0.88, P=0.01), respectively. Meanwhile, the survival curve of average daily dose decreased most heavily when it was >160 mg. They implied that high average daily dose of GC might be harmful to patients, especially in non-severe cases. While low average daily dose of GC was effective and decreased death risk by 47%-72% in severe cases.

This study showed that high dose GC at the beginning and the first three days prolonged the life of severe cases. Results from average daily dose proved that high dose GC increased the death risk of non-severe cases and low dose decreased the death risk of severe cases. They were not contradictory, because average daily dose was calculated by dividing by duration of admission which was 26 days on average in this study. Meanwhile, not only daily dose is necessary, but the duration of treatment, which can be partially measured by accumulated dose, is of importance as well. It was disclosed that -3000 mg, -6000 mg, and >6000 mg of accumulated doses could decrease risk of death by 52% (P=0.00), 67% (P=0.00), and 78% (P=0.00) in severe cases, respectively. The dose-response relationship showed the bigger accumulated dose, the better effects in severe cases. With the overall results from this study, it could be concluded that high dose GC, which should be used as double of first dose or pulse therapy, should be prescribed to severe patients at early stage of infection to control clinical progress and alleviate symptoms, while long-term treatment cannot be adopted. It was noteworthy that clinicians should take patients' conditions, daily dose, and duration of treatment into consideration carefully when deciding whether using GC or not and how to use it in treating MERS related ALI and ARDS.

The findings from this study highlighted the GC therapy in SARS patients in terms of the daily doses and accumulated doses, which provided references for clinicians in treating MERS related ALI or ARDS patients. But it should be kept in mind that although experience learnt from the SARS treatment is able to be applied when treating MERS related patients, severe symptoms and death caused by viruses are different. MERS-CoV was found to be 50-100 times more sensitive to IFN-α treatment than SARS-CoV [15, 28, 29]. The first limitation of this study lies that the comparison of treatment effects between two viruses is not conducted. Secondly, the design of this study is retrospec-

tive. Much more efforts need to be made to explore more appropriate administration of GC in treating MERS related ALI or ARDS patients, and recommendation of GC still need to be confirmed by double-blind randomized clinical studies. It is expected that the current study can draw adequate attention from researchers and clinical practitioners so that they would strive to collect related evidence and to conduct related researches, which is vital to provide guideline for correct usage of GC and decrease case fatality rate of MERS patients.

Conclusions

In summary, GC therapy was examined and analyzed by using different statistical models, with confounding factors adjusted in this study based on a database of a much larger sample size. Better therapies on daily and accumulated doses of GC usage in severe and non-severe SARS patients were screened, which will be helpful when clinicians make decisions on MERS treatment. Although MERS and SARS are different viruses, both of them are coronavirus and their core subdomains are homologous and similar in structures [4]. Meanwhile, the current therapeutic options for MERS are based on the experience from SARS [6, 12]. Therefore, results from this study might be one of the important references for MERS treatment.

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Disclosure of conflict of interest

None.

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