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Original Article

Every 10-fold increase in viral load results in 26% more patient deaths: a correlation analysis

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Abstract: In recent years, highly pathogenic viruses have seriously threatened human health. However, it remains controversial whether viral load is the determinant for high mortality of patients. The purpose of this correlation analysis was to study the quantitative association between viral load and mortality rate following viral infections. We conducted a literature search of peer-reviewed publications in electronic databases from inception to June 30, 2018. To normalize the data, viral load ratios (log_{10}) of non-survivors to survivors were calculated. In total, 47 valid data pairs of viral load ratio of non-survivors to survivors and the corresponding mortality rate were obtained. We calculated the possible linear regression between log_1, log_2, or log_{10} (viral load ratio) and the mortality rate. Only log_{10} (viral load ratio) had a good correlation ($R^2 > 0.5$; $P < 0.05$). For all 47 valid data pairs, the following regression equation was obtained: "$y = 3.776x + 0.200$". The regression equation suggested that, on average, a 10-fold increase in viral load would cause a 26% increase in the mortality rate. It can be deduced that a 10^4-fold increase in viral load would lead to almost 100% patient deaths. Hence, for the first time, we showed a quantitative association between viral load and the mortality rate. Our findings imply that antiviral therapies and anti-inflammatory treatments would be more effective if they are applied in the early stage of infection when the viral load has not reached the high-risk level.

Keywords: Highly pathogenic viruses, linear regression, mortality rate, quantitative correlation, viral load

Introduction

During the last decade, an endless stream of highly pathogenic viruses has emerged, which seriously threatens human health. The mortality rate due to these highly pathogenic viruses ranges from 3.6% to over 70% [1-3]. However, there has been some dispute whether the viral replication level is the key risk factor for high mortality. Some reports have shown that higher viral RNA levels are associated with the fatal outcome [4-6]. However, some reports indicated that there is no correlation between viral copies and mortality rates [7]. In some cases, the average viral load in non-survivors is lower than that in survivors [8, 9]. The purpose of this correlation analysis was to study the relationship between viral load and mortality rate following a viral infection. Only acute infections caused by highly pathogenic viruses and the immediate mortality rates were included in this analysis. Cases of mild viral infections associated with very low mortality rates (like seasonal flu viruses) or long-term viral infections with indirect mortality data (such as the human immunodeficiency virus) were beyond the scope of this correlation analysis.

Materials and methods

Data sources, search strategy and selection criteria

We conducted a literature search of peer-reviewed publications in electronic databases from inception to June 30, 2018. The three main

databases used in the search procedure were PubMed, Embase, and ISI Web of Science. Only acute infections caused by highly pathogenic viruses (listed below) and the immediate mortality rates were included in this analysis. The following three sets of keywords were employed for the literature search: keyword 1: "fatal or survival or death", keyword 2: "load or titres or copies", and keyword 3: the individual virus name [Dengue virus (DENV), Ebola virus (EBOV), Eastern equine encephalitis virus (EEEV), Herpes simplex virus (HSV), Marburg virus (MARV), Middle East respiratory syndrome-coronavirus (MERS-CoV), Morbillivirus (MV), Severe acute respiratory syndrome-coronavirus (SARS-CoV), Saint Louis encephalitis virus (SLEV), Western equine encephalitis virus (WEEV), or Yellow fever virus]. These keywords were entered into the "All Fields" option in the databases. Through these searches, we obtained a total of 1541 results, irrespective of the language, date of publication, nationality, race, age, and gender. Two authors (SCJ and SY) independently screened the titles and abstracts to remove the ineligible studies. Disagreements were resolved by discussion. We retrieved the full text of the potentially eligible studies and examined full-text reports for further evaluation. In cases where there were multiple reports for the same study, we used the last published report. After screening for relevancy and duplication by reading the titles and abstracts, 296 results were obtained. During the subsequent full-text (including the supplementary materials) screening, articles without the viral load data from both fatal and non-fatal patients (animals) were excluded. Finally, 42 results met the criteria.

Data extraction and quality assessment

Mean viral load ratios of non-survivors to survivors for each virus were retrieved directly from the literature or were recalculated indirectly from values presented in the figures or tables in the literature. This was not a meta-analysis, and therefore, other information, such as first author's name, year of publication, country, language, population type, age of participants, gender, and design of studies, was not considered. The sample size (*n* value) for non-survivors was also recorded. In total, 49 data pairs of viral load ratio of non-survivors to survivors and the corresponding mortality rate were obtained. However, two data pairs were outliers with an uncertain sampling background or inaccurate measurements (see Note 9 and Note 12 to **Table 1** for details), and therefore, they were rejected from the subsequent regression analysis. 47 valid data pairs are listed in **Table 1** [1-45]. This was not a meta-analysis, and therefore, methodological quality and heterogeneity and reporting biases were not computed.

Data synthesis and statistical analysis

Different reports presented viral loads in different ways, such as cycle threshold (Ct) values of the real-time polymerase chain reaction (PCR) analysis, $\log_{10}$ viral RNA copies, or absolute viral titres. To normalize the data, viral load ratios ($\log_{10}$) of non-survivors to survivors were calculated.

For the 47 valid data pairs, we calculated the possible linear regression between $\log_1$ (viral load ratio), $\log_2$ (viral load ratio), or $\log_{10}$ (viral load ratio) and the mortality rate. Only $\log_{10}$ (viral load ratio) had a good correlation ($R^2 > 0.5$; $P < 0.05$). Then we compared the weighted linear regression model (based on the sample size for non-survivors) and the simple linear regression model to analyze the relationship between viral load and mortality rate. However, weighted regression obtained a very poor correlation ($R^2 < 0.25$; $P > 0.05$). Thus, we adopted simple linear regression only for the data pairs. The F-test was performed to determine whether the data pairs fit the regression model. The regression equation, the correlation coefficient, and the *P* value were acquired by using SPSS v19.0 and Microsoft Excel 2013.

Results

Study selection and data synthesis

We conducted a literature search of peer-reviewed publications in electronic databases from their inception to June 30, 2018. Through the searches with keywords and the virus name (as indicated in **Figure 1** and the "Methods" section), we obtained 3 to 285 results for each virus (a total of 1541 results). After screening for relevancy and duplication by reading the titles and abstracts, 0 to 42 results for each virus (a total of 296 results) were obtained. During the subsequent full-text (including the supplementary materials) screening, publi-

Table 1. Complete list of viral load ratios of non-survivors to survivors and the corresponding mortality rates

Virus name	Mortality rate	Viral load ratio of fatal to non-fatal (log_{10}; sample time)	Sample *size* (*n*)	Descriptions	Ref.
DENV-3	55%	4.6 (N.A.)	23	Dengue virus type 3 in Brazil, 2002	[10]
DENV-1	11%	0.2 (1-8 DAO)	10	Brazil, 1990 to 2013 (Note 1)	[11]
DENV-2	11%	2.5 (1-8 DAO)	10		
DENV-3	29%	3.0 (1-8 DAO)	10		
DENV-4	11%	1.8 (1-8 DAO)	10		
DENV	13%	1.9 (3-4 DIH)	6	4-14 year-old children in India, 2011 (retrieved from Figure S8)	[12]
EBOV	60%	1.1 (0-1 DIH)	51	Sierra Leone, Oct. 1 to Nov. 9, 2014	[13]
EBOV	58%	1.8 (1-5 DAO)	18	Sierra Leone, Dec. 2014 to Feb. 2015	[14]
EBOV	48%	2.3 (0-1 DIH)	12	Congo, 2014 (Note 2)	[15]
EBOV	53%	2.0 (1-9 DAO)	27	Uganda from Aug. 2000 to Jan. 2001	[16]
EBOV	53%	1.0 (4-7 DAO)	48	Ebola virus (Sudan species) patients in Uganda in 2000	[17]
EBOV	52%	0.8 (N.A.)	612	Liberia, Aug. 2014	[18]
EBOV	55%	1.1 (5-7 DAO)	46	Sierra Leone, Dec. 2014 to Apr. 2015 (Note 3)	[19]
EBOV	40%	2.2 (0-1 DIH)	253	Sierra Leone, Jul. to Dec. 2014	[20]
EBOV	59%	1.5 (3-5 DAO)	26	Guinea, Nov. 2014 to Jan. 2015	[21]
EBOV	51%	2.7 (0-1 DIH)	270	Sierra Leone, Jun. to Oct. 2014	[5]
EBOV	47%	1.6 (7-17 DAO)	8	Sierra Leone, Jan. to Mar. 2015	[22]
EBOV	43%	0.9 (0-1 DIH)	16	Guinea, Mar. to Apr. 2014	[23]
EBOV	74%	3.6 (1-5 DIH)	6	Sierra Leone, May to Jun. 2014 (recalculated from Figure S7)	[2]
EBOV	19%	1.1 (0-1 DIH)	5	U.S. and European hospitals, Aug. 2014 to Dec. 2015 (recalculated from Figures S6 and S7)	[24]
EBOV	48%	1.7 (0-15 DAO)	32	Gulu district of Uganda, 2000-2001	[4]
MARV	100%	5.9 (5-6 DPI)	6	Wild-type MARV does not cause disease in mice; the adapted virus resulted in 100% death	[25]
WEEV	100%	4.7 (in brain; 4-6 DPI)	10	The strain McMillan caused 100% mortality; while the strain Imperial 181 caused no mortality in mice	[26]
EEEV	100%	6.0 (in brain; 1-4 DPI)	5	Aerosol inoculations caused 100% mortality; while subcutaneous inoculations caused no death in mice	[27]
SLEV	100%	4.0 (in Raw 264.7 cells; 3 DPI)	3	The strain CbaAr-4005 caused 100% mortality; while the strain CorAn-9275 caused no mortality in mice	[28]
H1N1 2009	5%	-0.3 (1-7 DAO)	23	Singapore, May to Nov. 2009 (Note 4)	[9]
HIN1 2009	4%	-0.2 (0-13 DAO)	18	Hong Kong, May to Sep. 2009 (Note 5)	[8]
H1N1 2009	4%	0.6 (1-3 DAO)	4	India, 2009 (recalculated from Figure 1; Note 5)	[7]
H5N1 2004	72%	1.3 (nose; 5-11 DAO)	10	H5N1 in Vietnam, 2004 to 2005	[3]
	72%	1.6 (throat; 5-11 DAO)	13		
H5N1 2004	50%	1.3 (1-2 DIH)	3	H5N1 in Vietnam, 2004 to 2005 (recalculated from Figure 3)	[29]
H7N9 2013	28%	0.8 (1 DAD)	6	H7N9 patients in China, 2013	[30]
H7N9 2013	33%	1.0 (5-14 DAO)	4	H7N9 patients in China, 2013 (recalculated from Table 1; Note 6)	[31]
H7N9 2013	32%	0.6 (7-15 DAO)	6	China, April 2013 (recalculated from Table 2; Note 7)	[32]
HSV	27%	1.3 (7-21 DIH)	4	ICU, France, Jan. 2009 to Dec. 2012 (recalculated from Figure S1; Note 8)	[33]
HSV-1	24%	0.6 (0-1 DIH)	9	ICU, Italy, May 2013 to Jun. 2014	[34]
Neonatal HSV	11%	0.7 (0-1 DIH)	2	neonatal HSV infection in Japan, 2003 (recalculated from Figure 1)	[35]
HSV-1	33%	-0.4 (0-1 DBD)	14	France, 1998 to 2005 (Note 9)	[36]

HSV-2	34%	3.0 (7-18 DPI)	7	Inoculations to mice caused 34% of leg weakness and then death (recalculated from Figure 1)	[37]
Neonatal HSV	15%	1.1 (0-1 DIH)	4	Neonatal HSV infection in Japan, 2001; (recalculated from Figure 2; Note 10)	[38]
Neonatal HSV-1	10%	0.6 (0-1 DIH)	3	neonatal HSV infection in USA, 1993 to 2012 (recalculated from Figure 1)	[39]
Neonatal HSV-2	10%	0.4 (0-1 DIH)	2		
SARS-CoV	22%	1.4 (10-15 DAO)	24	Hong Kong, 2002 to 2003 (in stool samples; Note 11)	[40]
	22%	1.7 (10-15 DAO)	8		
SARS-CoV	18%	1.3 (10 DAO)	69	Hong Kong, 2002 to 2003 (in nasopharyngeal specimens; Note 12)	[41]
		4.5 (10 DAO)	25		
MERS-CoV	40%	0.6 (in nasopharyngeal swab samples; 0 DIH)	41	Saudi Arabia, 2014	[42]
MERS-CoV	36%	0.7 (in respiratory secretions; 2-8 DAO)	5	Korean, Jun. to Aug. 2015 (recalculated from Figure 2; Note 13)	[43]
MV	60%	1.8 (21 DPI)	5	Inoculations of Morbillivirus to ferrets	[44]

Virus name abbreviations: DENV, Dengue virus; EBOV, Ebola virus; EEEV, Eastern equine encephalitis virus; HSV, herpes simplex virus; MARV, Marburg virus; MERS-CoV, Middle East respiratory syndrome-coronavirus; MV, Morbillivirus; SARS-CoV, severe acute respiratory syndrome-coronavirus; SLEV, Saint Louis encephalitis virus; WEEV, Western equine encephalitis virus. Other abbreviations: ICU, Intensive Care Unit; DAD, days after (antiviral) drug treatment; DAO, days after the onset of symptoms; DBD, days before (antiviral) drug treatment; DIH, days in hospital; DPI, days post infection; N.A., (testing time was) not available. Note 1: fatality rates among persons with Dengue shock syndrome could be more than 10%. However, mortality rates of four DENV serotypes are not shown in this report. So we searched literature databases and found only one reference [45], which mortality data for all four DENV serotypes were used. Note 2: in this report, EBOV loads of fatal and non-fatal patients were not available. However, Ct values of patients with or without hemorrhagic signs were used instead. Note 3: this was the viremic peak value difference. Survivors reached their EBOV peak value earlier than non-survivors (day 5 versus day 7 after symptom onset, respectively). The mean peak value of viremia in survivors was lower than in non-survivors (7.46 vs. 8.60 $\log_{10}$). Note 4: no fatal cases were studied in this report; however, viral loads from severe cases were available. Note 5: only a few fatal and non-fatal individuals were studied, and thus the mortality rate should not be calculated based on this report. The global mortality rate for H1N1 2009 was about 3.6% [1]. Note 6: one recovered patient (patient #4) with aberrant high H7N9 viral load was excluded during the calculation. Note 7: to calculate H7N9 viral load for fatal and non-fatal cases, nasopharyngeal swab samples, sputum samples, and stool samples were mixed to obtain the mean Ct values. Note 8: HSV patients with pneumonia were collected (five survivors, four deaths). However, for HSV patients with hepatitis, only two survivors were found, and therefore not included. Note 9: death at 6 months was counted. However, 33% may not reflect the actual fatality rate caused by HSV infections directly. Furthermore, viral loads were detected at 0-1 days before the antiviral drug treatment. No information about the disease states of the patients at the sampling time was available. Therefore, these data were rejected. Note 10: for neonatal HSV detection in cerebrospinal fluid, only one sample from a dead patient was available (n = 1). Thus, the viral load in cerebrospinal fluid was not counted. However, the viral load data in serum were counted (n = 4). Note 11: SARS viral loads of survivals could only be detected in stool samples, but not in nasopharyngeal aspirates, serum, or urine. Note 12: SARS viral loads of survivors were barely detected (or in very low levels) in nasopharyngeal specimens and serum samples, therefore the viral loads of survivors cannot be accurately detected. Thus, the data of viral load differences between fatal and non-fatal patients (6.2 vs. 1.7 $\log_{10}$) were rejected. The viral load data of patients with and without diarrhea (3.1 vs. 1.8 $\log_{10}$) were collected instead. Note 13: from 2 to 8 days after the onset of symptoms, MERS viral loads of some survivors were barely detected (or in very low levels) in plasma samples. Thus, the viral loads in plasma were not counted. However, the viral load data in respiratory secretions were counted.

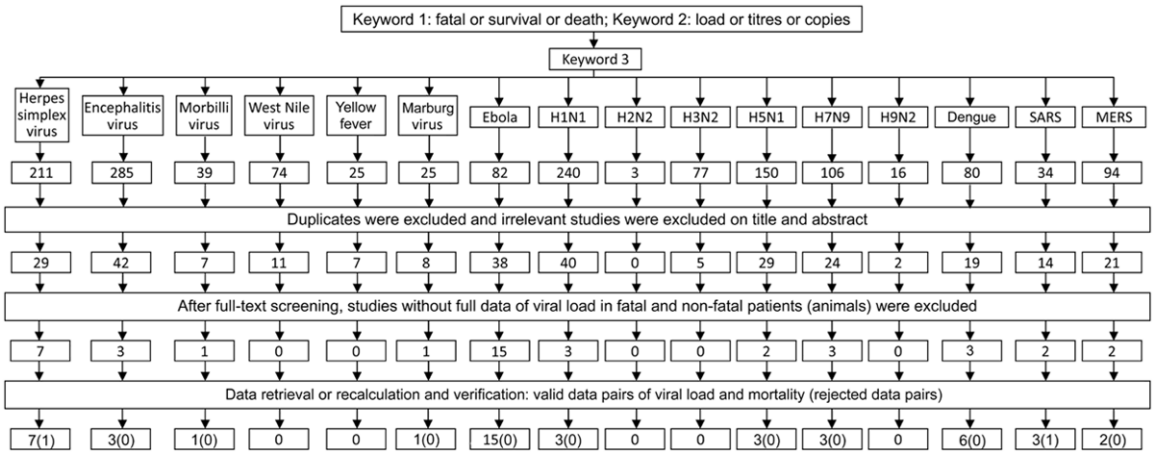

Figure 1. Flow chart algorithm for the literature search.

cations without the viral load data from both fatal and non-fatal patients (animals) were excluded. Finally, 0 to 15 results for each virus (a total of 42 results) met the criteria (**Figure 1**).

Preliminary analysis

In most of the cases, the average viral load in non-survivors was significantly higher than that in survivors. In some cases of 100% death, the viral load difference reached 10^4-10^6. However, there were two negative values of viral load ratios ($\log_{10}$), which suggested that the viral load in non-survivors was lower than that in survivors [8, 9]. These two cases were only reported in pandemic H1N1 (2009) infections, which had a global mortality rate of 3.6% [1]. In general, higher viral load differences correlated with higher mortality rates.

Correlation analysis

First, we calculated the possible linear regression between $\log_1$ (viral load ratio), $\log_2$ (viral load ratio), or $\log_{10}$ (viral load ratio) and the mortality rate. Only $\log_{10}$ (viral load ratio) had a good correlation ($R^2 > 0.5$; $P < 0.05$). Then we used both weighted linear regression (based on the sample size for non-survivors) and simple linear regression to analyze the relationship between viral load ratio ($\log_{10}$) and the mortality rate. However, weighted regression showed a very poor correlation ($R^2 < 0.25$; $P > 0.05$). By further examining the data, we found that the sample size (*n* value) varied tremendously among different reports, even for the same virus (*n* values ranged from 5 to 612 for the Ebola virus). Moreover, a larger sample size did not mean higher accuracy or greater representativeness. For example, Rosenke et al. [18] reported Ebola virus Ct values in 612 dead patients. However, no information about the sampling time or the disease state of the patients at the sampling time was available. Thus, weighted regression was not used, and we adopted simple linear regression only.

For all 47 of the valid data pairs, the following regression equation was obtained: "$y = 3.776x + 0.200$" (**Figure 2**). $R^2 = 0.507$ and $P = 1.98 \cdot 10^{-8}$ were obtained, which indicated that the data pairs fit the regression model. The regression equation suggested that, on average, a 10-fold increase in viral load would cause a 26% increase in the mortality rate. It can be deduced that a 10^4-fold increase in viral load may lead to almost 100% patient deaths (if $x = 100\%$, then $y = 3.976$). The intercept of 0.2 implied that for a viral infection with a very low mortality rate, the viral load in dead patients was still higher ($10^{0.2} \approx 1.6$ times) than that in convalescents. Individual regression equations were acquired for herpes simplex virus, Dengue virus, filovirus (Ebola virus and Marburg virus), and avian influenza virus (all $R^2 > 0.5$ and all *P* values < 0.05). By calculating the slopes, we estimated that a 10-fold increase in viral titres would result in 13%, 14%, 17%, and 47% increases in the mortality rate.

Variation analysis

The viral load data for a particular viral strain varied greatly among different reports. For

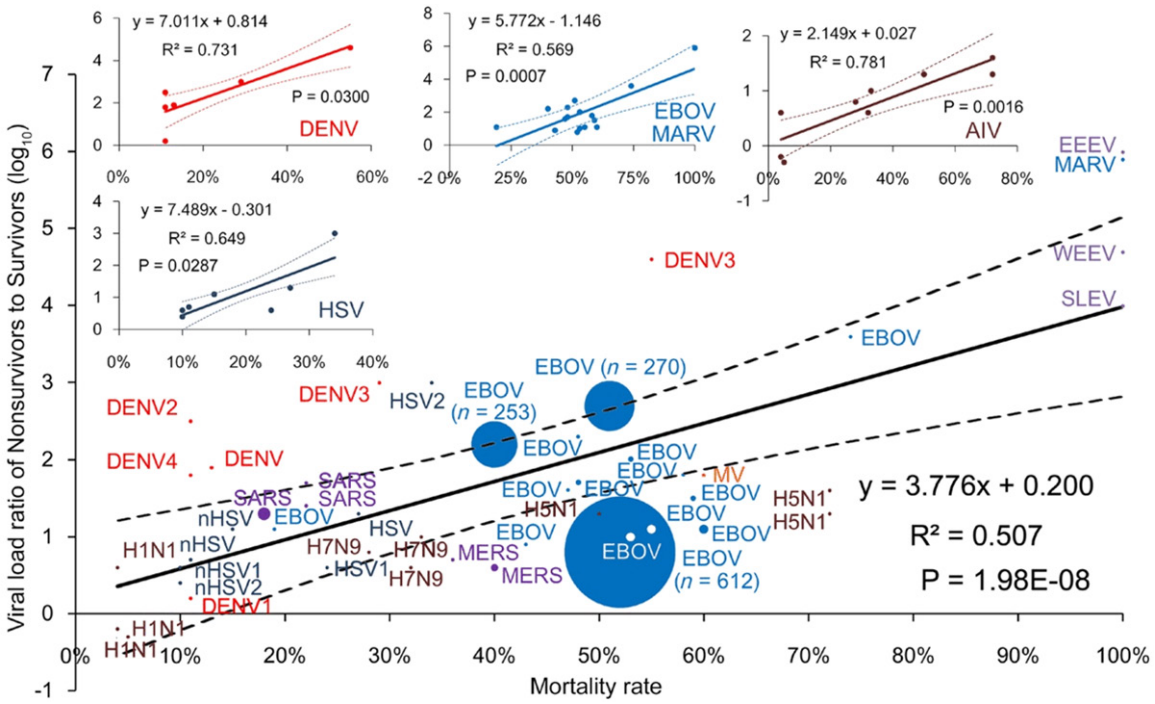

Figure 2. Correlation analysis between viral load and mortality. 47 valid data pairs of load ratio (log_{10}) of non-survivors to survivors and the corresponding mortality rate are included. Diameter of the data point represents the sample size of non-survivors (*n*). Dashed curves correspond to 95% confidence interval for the linear regression. DENV, Dengue virus; EBOV, Ebola virus; EEEV, Eastern equine encephalitis virus; HSV, herpes simplex virus; MARV, Marburg virus; MERS, Middle East respiratory syndrome-coronavirus; MV, Morbillivirus; SARS, severe acute respiratory syndrome-coronavirus; SLEV, Saint Louis encephalitis virus; WEEV, Western equine encephalitis virus.

example, for the Ebola virus strain Sierra Leone/2014 with a mortality rate of 47%-60%, viral load ratios (log_{10}) of non-survivors to survivors ranged from 1.1 to 2.7. The variations may be attributed to different sampling times. Most of the viral load values were investigated at admission (0-2 days in the hospital). However, they may have been assessed either 1-7 days or 7-17 days after the onset of symptoms. A time-course study by Lanini et al. suggested that at day 2 after the onset of symptoms, Ebola virus levels were significantly higher in non-survivors compared with survivors (0.94 log_{10}) [19]. This difference increased to 1.50 log_{10} and 4.94 log_{10} at day 7 and day 13 after the onset of symptoms, respectively. Survivors reached their viremic peak value earlier than non-survivors (day 5 versus day 7 after symptom onset, respectively). The mean peak value of viremia in survivors was lower than that in non-survivors (7.46 log_{10} vs. 8.60 log_{10}). Ideally, the viremic peak values of survivors and non-survivors should be compared; however, these data were not consistently available. Nonetheless, the available data points were sufficient to create a successful linear regression (P = 0.0007 and R^2 = 0.569 for Ebola virus and Marburg virus).

In addition to the sample collection time, the sample tissues also influenced the viral load ratio significantly. For instance, H5N1 viral load differences were 1.3 log_{10} and 1.6 log_{10} in nose and throat samples, respectively [3]. In another instance, SARS viral loads in survivors were only detected in stool samples but not in nasopharyngeal aspirates, serum, or urine; however, SARS viral RNA in non-survivors were always detected in all four tissue samples [40]. In principle, the largest difference among all sample tissues was recorded for each virus. Statistical analysis demonstrated that all the valid data fit the linear regression model ($R^2 > 0.5$; $P < 0.05$).

Discussion

Infection with highly pathogenic viruses causes multiple complications in the patient, resulting in multi-organ failure, and it may trigger a hyperimmune response to the virus, which may con-

sequently have adverse effects on vital organs and result in high mortality [46-49]. When the virus replicates relatively slowly, the host immune system may show a moderate response; however, when the virus replicates rapidly, the excessive viral load may set off a cytokine storm, resulting in a hyper-immune response to the virus and death [46-49].

To reduce the mortality rate, antiviral therapies should be initiated in the early stage of infection, ideally before the viral load reaches the high-risk level. Uyeki et al. followed 27 Ebola virus disease patients, who received treatments (including non-convalescent blood transfusion) in the U.S. and European hospitals from 2014 to 2015 [24]. The mortality rate reduced from 54% (43%-74% as shown in **Table 1**) to 19% (after the treatments), while the viral load ratios (log_{10}) of non-survivors to survivors reduced from a median of 1.7 (0.8-3.6 as shown in **Table 1**) to 1.1 (after the treatments) [24]. In another study, six persons who had occupational exposures to the Ebola virus in West Africa received the investigational agent rVSV-ZEBOV (rVSV-vectored vaccine expressing Ebola surface glycoprotein) or TKM-100802 (a lipid-bound small interfering RNA) for post-exposure prophylaxis [50]. All of the patients experienced self-limited symptoms after post-exposure prophylaxis; none had PCR evidence of Ebola virus infection, and none developed Ebola virus disease [50], implying the importance of early antiviral treatments.

Alternatively, if an effective antiviral therapy is not available, supportive care or anti-inflammatory agents should be administered in the early stage of infection. Qin et al. found that Ebola virus disease survivors had shorter periods between the time of onset of symptoms and the first clinic visit (4.6 ± 2.8 days) than non-survivors (6.3 ± 3.3 days) [51]. A 2-day delay in making a hospital visit did not result in significant differences in viral load, cytokine levels, or lymphocyte levels. However, a 2-day delay in making a hospital visit may result in 1.5-fold higher levels of D-dimer in fatal cases, suggesting a rapidly developing hemorrhage [52]. Although there are currently no treatments for EBOV infection, supportive clinical care may directly or indirectly restore dysregulated hemostasis. Similarly, an interesting study indicated that immuno-modulators significantly reduced mortality in mice infected by high inoculum of influenza H5N1 virus. The immuno-modulators did not significantly change the viral titres; however, they increased the survival rate from 13.3% to 53.3% [46]. These drugs suppress the cytokine storm, thus preventing cell death and vital organ failure.

This study has several limitations. First, not all of the highly pathogenic viruses were included in this analysis because of the lack of detailed data on viral load ratios of non-survivors to survivors, such as Yellow fever virus, as indicated in **Figure 1**. Second, mild viral infections with very low mortality rates (like seasonal flu viruses) were not included in this analysis because of the lack of data pairs of viral load ratios of non-survivors to survivors. The intercept of 0.2 was only the theoretical value calculated from the regression equation. Third, for viruses associated with 100% mortality rate, data pairs of viral load ratios of non-survivors to survivors were only recorded in the animal model experiments; no clinical data in humans were available. Fourth, in some reports, no information about the sampling time or the disease state of the patients at the sampling time was available. However, the sample size (*n* value) may have been very large. Thus, weighted regression was not used, and we adopted simple linear regression only. Fifth, the sample collection times and the sample tissues varied largely among different reports. Ideally, the viremic peak values of survivors and non-survivors in the most sensitive tissues should be compared; however, these data were not consistently available. Nonetheless, statistical analysis demonstrated that all of the valid data fit the linear regression model.

Conclusion

In this correlation analysis, we collected data pairs of viral load ratios (log_{10}) of non-survivors to survivors and mortality rates through literature search and recalculation. Statistical analysis indicated that the data pairs fit the linear regression model. In general, a 10-fold increase in the viral titres results in a 26% increase in the mortality rate. Our findings imply that antiviral therapies and anti-inflammatory treatments would be more effective if they are applied in the early stage of infection when the viral load is not very high.

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Disclosure of conflict of interest

None.

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