Case fatality of SARS in mainland China and associated risk factors

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Summary

OBJECTIVE To analyse the case fatality ratio (CFR) and its risk factors for severe acute respiratory syndrome (SARS) in mainland China by using a comprehensive dataset of all probable cases.
METHODS The data of all probable SARS cases were derived from the Infectious Disease Reporting System of the Center of Diseases Control and Hospital Information Systems, during the 2003 epidemic in mainland China. The definition of probable SARS case was consistent with the definition for clinically confirmed SARS issued by the Ministry of Health of the People's Republic of China. We performed univariate and multivariate logistic regression analysis to determine the association of CFR with age, sex, residence location, occupation, the period of the epidemic and the duration from symptom onset to admission into hospital.
RESULTS The overall CFR was 6.4% among 5327 probable SARS cases in mainland China. Old age, being a patient during the early period of a local outbreak, and being from Tianjin led to a relatively higher CFR than young age, late stage of a local outbreak and cases from Beijing. Guangdong Province resulted in an even lower CFR compared with Beijing.
CONCLUSIONS Because of their deteriorated health status and apparent complications, SARS patients aged >60 years had a much higher risk of dying than younger patients. At the early stage of local outbreaks, lack of experience in patient care and perhaps treatment also led to a relatively higher CFR. The Tianjin SARS outbreak happened mainly within a hospital, leading to a high impact of co-morbidity. The relatively young age of the cases partly explains the low CFR in mainland China compared with other countries and areas affected by SARS.

keywords case fatality ratio, China, risk factors, severe acute respiratory syndrome

Introduction

WHO reports about the global epidemic of severe acute respiratory syndrome (SARS) showed that the case fatality ratio (CFR) in mainland China was about 6%, considerably lower than in other affected countries and areas such as Hong Kong and Toronto, where the CFR was about 17% (Feng *et al*. 2009). Proper identification of risk factors for the CFR may explain this striking difference. However, there has never been a report using the overall data of Chinese cases to describe and analyse the CFR. Published articles on CFR only reported results for different Chinese provinces such as Hong Kong (Karlberg *et al*. 2004), Beijing (Chen *et al*. 2005), Guangdong (Peng *et al*. 2003), Shanxi (Mei *et al*. 2003), Tianjin (Wang *et al*. 2003a) and

Inner Mongolian Autonomous Region (Tao *et al*. 2003). Although some general conclusions were put forward such as the strong association with old age, some results, such as the contribution of sex, were controversial (Karlberg *et al*. 2004; Chen *et al*. 2005). In addition, it was difficult to predict the risk of death for SARS patients because of the limited data based on individual regions and without taking the overall epidemic in mainland China into consideration. The previous publications were further limited; in that, some important parameters (e.g. period of the epidemic) were not included and often only univariate regression analysis was performed on the data (Chen *et al*. 2005). In addition, as SARS-related reports were required as soon as possible during the emergent epidemic, it is understandable that some data were not yet

available in the early reports. For a full insight into the epidemiological features of the epidemic, it was necessary to carefully organise all available information from mainland China in one comprehensive database (Feng *et al.* 2009).

In this paper, we describe and analyse factors associated with CFR for SARS, using the comprehensive database covering all regions of mainland China, and in particular explain why case fatality was so much lower in mainland China compared with most other affected countries and areas in the world.

Methods

Sources of data

Information was collected of all probable SARS cases, derived from the Infectious Disease Reporting System of the Centre of Diseases Control and Hospital Information Systems, during the 2003 epidemic in mainland China, and integrated into a final database. Based on the various sources, we completed a database with 5327 probable SARS cases after record cleaning, exclusion of duplicate cases and completion of missing information (Feng *et al.* 2009). The database contains information of individual cases with SARS throughout the 2002–2003 epidemic, i.e. demographic factors, location of residence, onset date, admission date, discharge date, date of death and outcome (fatal or survival) of cases.

Definition of SARS

The definition of a probable SARS case was consistent with the case definition for clinically confirmed SARS issued by Ministry of Health (MOH) of People's Republic of China (Feng *et al.* 2009). Although laboratory tests of SARS were available during part of the duration of the outbreak, not all cases were tested, especially those in the earlier stage of the epidemic. Additionally, the sensitivity and specificity of the laboratory test were unknown because there were no 'gold standard' laboratory or clinical pathologic definitions for the diagnosis of SARS during the epidemic in 2003 (Leung *et al.* 2004).

Statistical analysis

Probable cases with SARS were categorised by the following risk factors: age (in 10 years), sex, location of residence, occupation, period of the epidemic (in 30 days) and the duration from symptom onset to admission to hospital. Location of residence concerned the five most affected areas (Guangdong Province, Shanxi Province, Beijing, Tianjin and Inner Mongolia Autonomous Region)

and other areas. Occupation was classified into three main groups: (i) healthcare worker (HCW), (ii) high economic status (HES) worker (i.e. businessman, civil servant or teacher) and (iii) low economic status (LES) worker (farmer, day-care worker/nanny, waiter/waitress or worker). 'Unknown' was used if occupation was not recorded. Children, retired people and students ('other') were not considered as a special group because of the high correlation with age, and treated as missing in univariate analysis. The period of the SARS epidemic in mainland China was defined by the calendar date of the onset of symptoms since the first SARS case (16 November 2002) in Guangdong Province.

Univariate logistic regression analysis was performed to identify the association between CFR and the above risk factors. Continuous variables were tested both categorically and continuously. In addition, we tested adding an age-squared and using log-transformation for age. All variables of the univariate analysis with significance $P < 0.20$ were subsequently entered into a multivariate logistic regression model. Here, occupation was only included as being HCW or non-HCW, and the latter group included the categories 'Unknown' and 'Other', because we assumed that all HCWs were correctly recorded. The software package used for the analysis was SPSS, version 10.0 (SPSS Inc., Chicago, IL., USA).

Results

Of 5327 probable cases with SARS, 343 cases died, giving an overall CFR of 6.4% (Table 1). The CFR of females (5.6%) was slightly lower than that of males (7.2%). Table 1 also shows that CFR increased dramatically with age, leading to the risk of dying among cases aged 60 years and older being 10 times higher than among cases younger than 40 (about 25% *vs.* 2%). The CFR of HCW (3.3%) was by far the lowest among all occupational groups. The cases in Guangdong Province (3.6%), and to a lesser extent Shanxi (5.4%), had the lowest risk of dying from SARS, whereas Tianjin showed the highest CFR (12.0%). Beijing (7.3%) and the other areas showed average values. Figure 1 reveals that the difference between levels of CFR in Tianjin (highest), Beijing (moderate) and Guangdong (lowest) is fully explained by the difference in fatality for cases of 50 years and above. SARS cases with a younger age all had an equally low case fatality. Duration from onset to admission does not associate with CFR (Table 1). In addition, CFR does not seem to show a particular trend with period of the epidemic (Table 1); however, when plotted for different geographic locations, it becomes clear that CFR has reduced consistently over time

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Table 1 Risk factors for dying because of SARS in mainland China derived from univariate and multivariate logistic regression

Risk factor	Probable cases	Deaths (CFR%)	Univariate		Multivariate	
			Crude odds ratio (95% CI)	*P*-value	Odds ratio (95% CI)	*P*-value
All	5327	343 (6.4)				
Sex						
Female	2607	147 (5.6)	1.00	–	1.00	–
Male	2720	196 (7.2)	1.30 (1.04, 1.62)	0.020	0.81 (0.64, 1.02)	0.072
Age (categories)						
0–19 years	476	8 (1.7)				
20–39 years	2844	70 (2.4)				
40–59 years	1457	130 (8.9)				
60–79 years	486	124 (25.5)				
80–93 years	62	11 (17.7)				
Age (continuous, 10 years)			1.80 (1.69, 1.92)	<0.001	1.86 (1.74, 2.00)	<0.001
Occupation*				0.006		
HCW	1021	34 (3.3)	0.55 (0.37, 0.82)	0.003	0.76 (0.52, 1.15)	0.18
Non-HCW	(4306)	309 (7.2)	–	–	1.00	–
HES	644	43 (6.7)	1.14 (0.79, 1.65)	0.47		
LES	1834	108 (5.9)	1.00	–		
Unknown	793	51 (6.4)	1.10 (0.78, 1.55)	0.59		
Others	1035	107 (10.3)	–	–		
Location				<0.001		<0.001
Beijing	2522	184 (7.3)	1.00	–	1.00	–
Tianjin	175	21 (12.0)	1.73 (1.07, 2.80)	0.025	1.79 (1.07, 2.99)	0.027
Guangdong	1504	54 (3.6)	0.47 (0.35, 0.65)	<0.001	0.13 (0.08, 0.23)	<0.001
Shanxi	449	24 (5.4)	0.72 (0.46, 1.11)	0.14	0.71 (0.45, 1.13)	0.15
Inner Mongolia	282	28 (9.9)	1.40 (0.92, 2.13)	0.11	1.34 (0.86, 2.08)	0.19
Other provinces	395	32 (8.1)	1.12 (0.76, 1.66)	0.57	1.30 (0.86, 1.98)	0.21
Period of the SARS epidemic (categories)						
November–December	19	1 (5.3)				
January	164	14 (8.5)				
February	745	23 (3.1)				
March	546	44 (8.1)				
April	3198	229 (7.2)				
May	655	32 (4.9)				
Time since the first SARS case (continuous, 30 days)			1.08 (0.97, 1.21)	0.16	0.59 (0.48, 0.71)	<0.001
Duration from onset to admission						
0–1 days	1758	115 (6.5)				
2–3 days	1401	81 (5.8)				
4–5 days	835	56 (6.7)				
6–7 days	617	46 (7.5)				
8–9 days	263	19 (7.2)				
10–11 days	160	16 (10.0)				
≥12 days	267	10 (3.7)				
Missing	26	0 (0.0)				
Duration from onset to admission (continuous, days)			1.00 (0.97, 1.02)	0.80		

*In univariate analysis, occupation has been divided into four groups: HCW is health care worker; HES is high economic status such as businessman, civil servant and teacher; LES is low economic status such as farmer, day-care worker/nanny, waiter/waitress and worker. 'Others' includes three groups with a strong correlation with age, i.e. retired people, students and children, and these were not considered in univariate analysis. In the multivariate logistic regression model, only two groups have been introduced: HCWs and all non-HCWs combined.
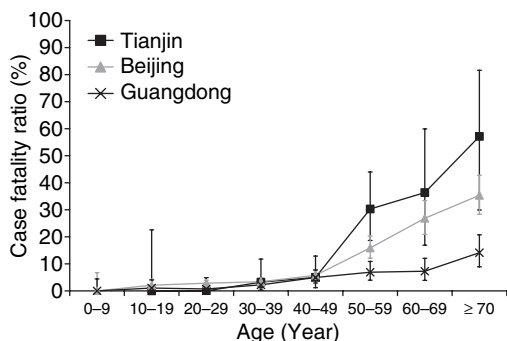
Figure 1 Comparison of the case fatality ratios for SARS patients in Beijing, Guangdong and Tianjin with age. Intervals indicate 90% binomially distributed confidence intervals.

(Figure 2). Strikingly, Guangdong showed an increase in CFR about 3–4 months after onset of the epidemic.

In univariate logistic regression, CFR because of SARS is only significantly associated with age, sex, occupation and location (Table 1). Multivariate logistic regression shows that age and location remain significantly associated with CFR, also after correction for the other variables. However, the significant effect of occupation (HCW *vs.* non-HCW) disappeared, whereas that of sex seemed to reverse by showing an almost significantly higher risk for females. Clearly, the relatively low CFR for females and HCWs was largely because of relatively young age of many of these cases. As Figure 2 illustrates, the period of epidemic shows a significant decreasing effect in the multivariate model after adjusting for other factors, in particular geographic location (Table 1). The interaction of period of epidemic and location was not significant

($P = 0.334$), indicating that the downward trend in CFR is about equal for each geographic location.

Discussion

This report gives the first complete insight into the factors associated with risk of death of SARS patients in mainland China. The overall CFR was 6.4% among the cumulated 5327 probable SARS cases. Old age, being a patient during the early period of epidemic and cases from Tianjin had a higher CFR compared with young age, late stage of the epidemic and cases from Beijing and other areas. Cases from Guangdong had the lowest CFR in mainland China.

The initial reports (Mei *et al.* 2003; Peng *et al.* 2003; Tao *et al.* 2003; Wang *et al.* 2003a; Karlberg *et al.* 2004; Chen *et al.* 2005; Liu *et al.* 2006; Feng *et al.* 2009) as well as the current paper demonstrated that older SARS patients had a much higher fatality ratio compared with younger patients. This may largely be due to the fact that many elderly patients had chronic diseases, and when they suffered from SARS, their health condition deteriorated easily. This was amplified by the relatively higher number of old people who contracted SARS in the hospital while suffering from life-threatening other morbidity. The presence of co-morbid conditions is associated with poor outcomes, such as death, ICU admission and mechanical ventilation of SARS patients (Booth *et al.* 2003; Chan *et al.* 2003; Fowler *et al.* 2003; Peiris *et al.* 2003; Wong *et al.* 2003; Gomersall *et al.* 2004). Unfortunately, co-morbidity and place of contracting the infection (i.e. hospital or not) were not recorded in the final database.

So far, only one published Hong Kong report indicated a gender difference in SARS CFR: males had a significantly
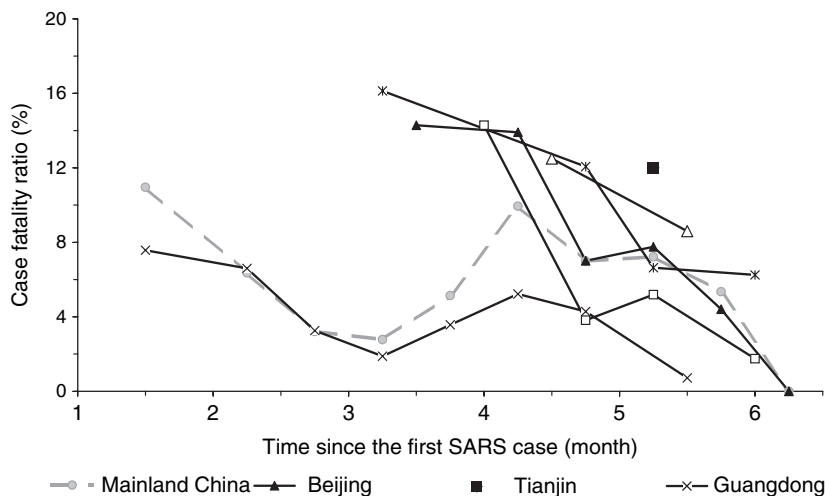

Figure 2 Comparison of the case fatality ratios for SARS patients in different locations with the number of months since the first SARS case emerged in mainland China (i.e. 16 November 2002). Every marker has been based on at least 40 SARS cases and represents a half-month period, or somewhat longer for the end points of some lines.

higher CFR than females, 21.9% *vs.* 13.2%, which remained significant after correction for age (Karlberg *et al.* 2004). Reports from other different provinces showed no significant association of sex with CFR (Mei *et al.* 2003; Peng *et al.* 2003; Tao *et al.* 2003; Wang *et al.* 2003b; Chen *et al.* 2005). Our large database also suggests that gender does not play an important role. The initial higher risk of dying among males was reversed into a borderline statistically significant higher risk for females after correction for other factors. Still, if anything, the risk for females is only slightly higher than for males (OR = 0.83).

Healthcare workers were major victims during the SARS epidemic. For Hong Kong and Taiwan, it was reported that HCWs had a lower CFR than non-HCWs (2.0% *vs.* 21.8% and 11.4% *vs.* 25.3%, respectively; Leung *et al.* 2004; Chang *et al.* 2006). In our study of mainland China, HCWs also showed a much lower CFR than non-HCWs (3.3% *vs.* 6–10%). From multivariate analysis, however, it turned out that being HCW or not was not a significant factor anymore. Apparently, the low CFR among HCWs can fully be explained by their relatively young age. HCW factor was also not significant after correction for age in the reports from Hong Kong and Taiwan. Thus, HCW apparently did not benefit from being closer to rapid and appropriate health care.

The CFR in Tianjin was significantly higher than in Beijing, whereas the CFR in Guangdong was significantly lower than in Beijing. First of all, the cases in Tianjin were older than in other parts of China (median age of 42 *vs.* 33 years). In addition, after correction for age, however, cases in Tianjin of over 50 showed a higher risk of dying than in Beijing and Guangdong. The high CFR in Tianjin may be due to the special situation that 120 out of 175 cases (68.6%) were hospital inpatients (Wang *et al.* 2003a). This percentage is unknown for other areas in China, but the proportion of HCW cases among all SARS cases in Tianjin is also much higher than for other areas (39% *vs.* 19%), also illustrating the high rate of nosocomial infection in this city. Thus, the general lower health status of these hospitalised Tianjin cases may be the major explanation for the high mortality risk. The fact that geographic differences were only present for age group older than 50 years further supports that the degree of being hospitalised at the time of infection was an important factor.

Guangdong Province was the source region of the SARS outbreak and failed to contain the disease, whereas epidemics in other provinces all resulted from importation from Guangdong. It is not known whether a possible cumulated virulence of the virus in import cases lead to more serious symptoms of patients in import locations

(Zhao 2007), which could explain the lowest CFR in Guangdong. It is striking that even in its first months, Guangdong showed a lower CFR (6–8%) than the first months in other provinces (12–16%). We have no clear explanation for this finding, but it has been suggested that over-reporting of SARS cases may have been a problem in Guangdong (Chen *et al.* 2004); the use of particular traditional Chinese medicine (Zhong 2004), and even air pollution (Cui *et al.* 2003) may have played a role.

We expected that the duration from onset to admission could have contributed to the CFR as one report suggested (Chen *et al.* 2005), but we found no such correlation in our data. Clearly, being in the hospital earlier, and probably with a better condition, did not improve the prognosis of an SARS patient. This was also shown in one analysis of Beijing SARS patients, where in cases without chronic baseline diseases, the age-standardised fatality rates were not associated significantly with the delayed hospitalisation (Wu *et al.* 2004).

One of the most striking findings is that the CFR decreased substantially with the time of the epidemic for all geographic locations. In Beijing, where SARS was present until 6 months after the first case, CFR even decreased to 0. Apparently, care had improved substantially during the course of the epidemic, and the experience of treatment, not only of the immediate symptoms of the SARS virus infection itself, but also the management of prevention of complications had been optimised. In addition, in the later stages of the epidemic, all SARS cases were hospitalised in a hospital designated specially for SARS with accepted standard treatment, which may also have substantially contributed to the much better survival of patients.

From the discussion above, we can identify some factors that may explain why the SARS CFR in mainland China was so much lower than in other areas of the world. First, the SARS cases in China had a relatively younger age (median 33 years) than in other areas, e.g. Hong Kong (40), Taiwan (46) and Canada (49); (Feng *et al.* 2009). Consequently, the proportion of individuals at higher risk of dying (i.e. those of 50 years and above) is also higher in these areas. Using the age-related CFR values of mainland China (as resulted from our study) for the age distributions of SARS cases in Hong Kong and Canada resulted in an expected overall CFR of about 9.2% (data not shown). This is indeed higher than the overall value in mainland China (6.4%), but still much lower than the actual values of 17.2% and 17.1% in Hong Kong and Canada, respectively. Thus, the relatively young age of Chinese SARS patients can only partly explain their low case fatality.

Second, the lower CFR in mainland China is partly explained by the particularities of the epidemic in

Guangdong (low CRF), although the reasons for the very low case fatality remain unclear. Third, the CFR in all provinces (apart from Guangdong) started with levels comparable to the average CFR in other areas (about 12–16%; Figure 2), but fell over time as a result of improved care. In many areas, the epidemic may not have lasted long enough to establish the same improvement. Nevertheless, it seems that all factors in combination are not a sufficient explanation for the low CFR of SARS cases in mainland China.

In our analysis, we used the typical calculation of CFR, that is, dividing the number of deaths by the total number of cases. This simple method is accurate once the epidemic is complete. A new method to evaluate CFR has been developed, which is more adequate throughout the early and middle stages of epidemic (Galvani *et al.* 2003; Ghani *et al.* 2005; Jewell *et al.* 2007).

In conclusion, the overall CFR because of SARS was 6.4% in mainland China. CFR increased markedly with age and decreased as the epidemic progressed in every geographic location. CFR values were relatively highest in Tianjin, probably because of more co-morbidity, and lowest in Guangdong. The relatively young age of SARS cases in China partly explains the difference with CFR in other affected areas.

Acknowledgements

Conflicts of interest

The authors have declared that they have no conflicts of interest.

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