Frailty increases incidence risk of infection in the elderly: A population-based cohort study

Ya Yang, Kechun Che, Jiayan Deng, Xinming Tang, Wenyuan Jing, Xiuping He, Jiacheng Yang, Wenya Zhang, Mingjuan Yin, Congcong Pan, Xiaoling Huang, Zewu Zhang, Jindong Ni

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Abstract

Background: nfectious diseases are among the leading causes of death and disability. As the population ages, it faces an enormous challenge with frailty.Nevertheless, there are only few prospective assessments on the association between frailty with infectious disease. Hence, research on frailty and infection is urgently needed.

Objective: we aimed to examine the associations of frailty and infection disease.

Methods: We conducted a prospective follow-up study of 11,930 elderly Chinese, dividing them into frail and healthy groups at baseline. Incidence data for infectious diseases were collected through the Chinese Disease Control and Prevention Information System – Infectious Disease Monitoring and Public Health Emergency Monitoring System. A questionnaire survey was used to assess frailty status. We compared the incidence rate ratio (IRR) of each disease stratified by age and sex. Cox proportional hazards regression was conducted to identify the effect of demographic factors and frailty on the risk of infectious diseases, with estimations of the hazard ratio (HR) and 95% confidence interval (CI).

Results: A total of 235 cases of 12 infectious diseases were reported during the study period, with an incidence of 906.21/100,000 person-years in the frailty group. In the same age group, the risk of infection was higher in men than women. Frail elderly had an HR for infectious diseases of 1.50 (95% CI: 1.14–1.97) compared with healthy elderly. We obtained the same result after sensitivity analyses. For respiratory tract transmitted diseases (IRR: 1.97, 95% CI: 1.44–2.71) and gastrointestinal tract transmitted diseases (IRR: 3.67, 95% CI: 1.39–10.74), frail elderly are at risk. Whereas no significant association was found for blood-borne, sexually transmitted and contact- transmitted diseases(IRR:o.76, 95%CI: 0.37-1.45).

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Frailty increases incidence risk of infection in the elderly: A population-based cohort study

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Conclusion: our study provides additional evidence that frailty components are significantly associated with infection disease.Health care prfessional should pay more attention to frailty in infectious disease prevention and control.

Key words: Infectious Diseases; Community elderly; Frailty

Introduction

The COVID-19 pandemic plunged humanity into an infectious disease crisis. Over the previous centuries, global pandemics of infectious diseases periodically threatened the survival of entire populations, resulting in physical and psychological harm to patients and a huge economic burden on society. The battle with infectious diseases has never stopped. When facing a pathogenic invasion, the immune system is the key to survival. The immune system undergoes significant changes with age. These changes are collectively referred to as immunosenescence[1] . Disorders of the immune system can lead to vulnerability to infection, cancer, autoimmune illness, and vaccine failure[2] .

Frailty has been defined as a state of increased vulnerability to adverse health outcomes, secondary to multiple deficits in physiological, physical, and mental function[3]. Frailty significantly influences the elderly's regulatory T-cells and senescent natural killer cells, making them prone to infectious diseases[4]. Frail elderly people are more likely to be infected with fungi, bacteria, and viruses than the general population[5-7] . Studies have shown that frailty is associated with the attenuation of vaccine-induced responses to antibodies and an increase in post-vaccination influenza infections among community-dwelling older adults, and that vaccine effectiveness declines with increasing frailty[8, 9]. There is evidence that those aged 60 years and above are at the highest risk of dying from influenza, and that this risk increases with age[10] . A cohort study found increased risk of developing COVID-19 in the presence of frailty syndromes[11] .

At present, we are facing the dual threat of emerging and re-emerging infectious diseases. As the population ages, a new challenge is surfacing for societies: frailty. Current evidence suggests that frailty increases the risk of developing infections. However, there has been little investigation of this in China. Studying a population based sample of older adults categorized by their frailty status may help to untangle the relationship between frailty and infection. Thus, we conducted a population-based prospective and observational study focusing on frailty and infection. The results may help to disentangle the association between frailty and infections.

Methods

Study Population

we selected the elderly population from a frailty epidemiological survey in Dalang Town, Dongguan City, China, in 2018 and Guancheng Street, Dongguan City in 2020. We conducted non-interference follow-up on the study subjects every years. Trained investigators used a project-developed frailty assessment scale to conduct a questionnaire survey on elderly and collected basic information in the form of a one-on-one face-to-face survey. Including demographic, lifestyle and frailty statu. The survey methodology and data collection procedures were approved by institutional review board of the Guangdong Medical University. We included participants in the Guangdong Medical University cohort database who were aged ≥65 years, had complete data on basic information, frailty and morbidity, and had been followed up for at least one year as our study participants. Ultimately, 11,930 elderly individuals who met the inclusion criteria were included in the study cohort.

Ascertainment of frailty

The diagnostic criteria of the project-developed frailty evaluation scale were used as the basis for diagnosing frailty in this study. The evaluation was graded by calculating the scores of the debility assessment and analysis entries, with FI < 0.22 evaluated as healthy and FI ≥ 0.22 evaluated as frail. The scale is based on the frailty index model and contains 33 entries in seven dimensions, including general health status, ability to perform activities of daily living, functional activities, symptoms and signs, cognitive functioning, social support, and psychological status. Tests of the elderly population showed that the internal consistency reliability of the scale with Cronbach's α coefficient was 0.87, and the correlation coefficient between the score of the frailty index scale and the score of the frailty phenotype was 0.78 ($P < 0.001$). As such, its reliability was good[12].

Ascertainment of Infection

After collecting the baseline information, outcome events were tracked annually through follow-ups on the study’s subjects. The outcomes included statutory infectious disease incidence. We used the Chinese Disease Control and Prevention Information System – Infectious Disease Monitoring and Public Health Emergency Monitoring System to query and match people's statuses, as well as telephone for active follow-up until they suffered from infectious disease or until March 30, 2023, whichever came first. The primary outcome in this study was the incidence of infectious diseases. As of March 2023, it included two Class A infectious diseases and 27 Class B infectious diseases, totaling 40 kinds and excluding monkeypox, which was newly added in September 2023[13, 14].

Ascertainment of Covariates

Gender, age, educational level (illiterate, primary school, junior high school and above), smoking status (never, ever, yes), drinking alcohol status (everyday, more than once a week, occasional, never), physical activity level, and participation in community activities were obtained by interviews and physical examinations. physical activity level determined by grading the level of physical activity, including low, medium, and high intensity[15] . Participation in community activities is refers to participation in activities carried out in the community for the purpose of enriching the spiritual cultural life and social life of the residents, such as badminton, ping-pong, mah-jongg, chess, choir, dance troupes, and so on, including frequent, occasional and never.

Ethics Approval

Informed written consent was obtained from all participants included in this study,and the study was approved by the Research Ethics Committee of Guangdong Medical University (YJYS2018046).

Statistical Analysis

First, we conducted a descriptive analysis of the baseline characteristics. The demographics and lifestyles of people at various frailty levels were described. The counting data were presented in frequency and percentage form. Due to the different chronological order of entry into the cohort, each subject was observed for a different period of time. Therefore, person-years of follow-up were calculated on an individual basis. We use the chi- squared test to examine the differences between different levels of demographic data (age, gender, education level), lifestyle (participation in community activities, alcohol consumption, tobacco use, exercise) and morbidity data (frailty, incidence of infectious diseases). The temporal, regional, and population distributions of each infectious disease were described based on the incidence densities. Incidence rate ratios (IRRs) were used to compare the incidence densities of different populations for the same disease. The 95% confidence interval (CI) was used to determine whether the difference was statistically significant.

Next, we compared the risk of suffering infectious disease in two levels of frailty. We used the Cox regression model with stepwise adjustment of confounding variables to determine the risk ratio and 95% confidence interval for suffering infectious disease. Then, We excluded individuals with hepatitis B and C and tuberculosis to conducted sensitivity analyses to test the robustness of the result and to minimize potential reverse causation due to incubation period.

All statistical analyses were performed using SPSS (version 21.0) and MedCale (version 20.1.4), with 2-sided $P < 0.05$ was deemed statistically significant.

Results

Baseline information

Baseline information on the study cohort of 11,930 subjects is shown in Table 1. During the 35,658 person-years of follow-up, we recorded 235 cases of statutorily reported infectious diseases. The frailty and control groups showed significant differences in age distribution, gender ratio, education level, drinking alcohol status, physical activity level, and participation in community activities, but non-significant differences in smoking status.

Table 1. Baseline characteristics of patients.

Factor/group	control	frailty	total	χ^2	*P*
Age					
65-	6237	2429	8666	657.72	<.001
75-	1476	1255	2731		
85-	148	385	533		
Gender					
Men	3547	1304	4851	189.95	<.001
Women	4314	2765	7079		
Education level					
illiterate	717	947	1664	498.86	<.001
Primary School	3650	1842	5492		
junior high school	3494	1280	4774		
and above					
Smoking status					
never	5534	2911	8445	2.18	.34
ever	706	338	1044		
yes	1621	820	2441		
Drinking alcohol status					
everyday	247	102	349	47.23	<.001
more than once a week	141	66	207		
occasional	727	239	966		
never	6746	3662	10408		
Physical activity level					
Low intensity	1136	989	2125	215.61	<.001
Medium intensity	4524	2266	6790		
High intensity	2201	814	3015		
Participation in community activities					
frequent	1345	553	1898	33.56	<.001
occasional	950	438	1388		

never	5566	3078	8644		

Statutorily reported infectious diseases were categorized as blood-borne, sexually transmitted and contact-transmitted diseases, natural sources and vector-borne diseases, gastrointestinal-transmitted diseases and respiratory- transmitted diseases. A total of 12 statutorily reported infectious diseases were present in the cohort, and none were from natural sources or vector- borne diseases (Table 2).

Table 2. Number of cases of different classified diseases.

classification	name	numbers
Respiratory transmitted diseases	influenza	7
	mumps	2
	TB	15
	Covid-19 infection	142
Gastrointestinal-transmitted	The other infectious diarrhea[a]	21
Blood-Borne Sexually Transmitted and Contact Transmitted	HIV	1
	Viral Hepatitis (HBV, HCV)	24
	syphilis	18
	Condyloma acuminatum	1
	genital herpes	3
	Chlamydia trachomatis infection of the reproductive tract	1

[a]Refers to infectious diarrhea other than cholera, dysentery, typhoid and paratyphoid.

Frailty of different groups

Comparison of the incidence of infectious diseases in different groups, we found that the risk of infectious disease increased for people in frail group by 73% (IRR: 1.73, 95% CI: 1.33–2.25; see Table 3).

Table 3. Observations of different groups.

groups	total person-years	cases	incidence density(/ 100000 person-years)	IRR	95%CI
frailty	12579.8	114	906.21	1.73	1.33-2.25
control	23078.7	121	524.29		
total	35658.5	235	659.03		

Gender and age stratificated analyses

The incidence densities of men in all age groups were higher than those of women in the same age group, and the incidence densities of women increased with age. There were significant differences between men and women in the 65–74 year age groups (Table 4).

Table 4. Stratified Analysis by Gender and Age.

	Case		person-years		Incidence density		IRR		95%CI
Age	Men	Women	Men	Women	Men	Women	Men	Women	
Gender									
65-	62	59	10091	15233.30	614.41	387.31	1.59	1.00	1.09-2.31
75-	54	41	3437.90	5163.20	1570.74	794.08	1.98	1.00	1.29-3.04
85-	9	10	634.20	1098.90	1419.08	910	1.56	1.00	0.56-4.27

Frailty and infectious diseases

Frailty was associated with a higher risk of respiratory-transmitted diseases (IRR: 1.97, 95% CI: 1.44–2.71) and gastrointestinal-transmitted diseases (IRR: 3.67, 95% CI: 1.39–10.74; see Table 5).

Table 5. Impact Analysis of Infectious Diseases by Different Transmission Routes.

sмission	incidence density(/ 100000 person-years)		IRR	95%CI
	Frailty	Control		
piratory transmitted	683.64	346.64	1.97	1.44-2.71
rointestinal-transmitted	111.29	30.33	3.67	1.39-10.74
od-Borne, Sexually Transmitted	111.29	147.32	0.76	0.37-1.45
Contact Transmitted				

There were significant differences ($P < 0.05$) in baseline information between the two groups, including gender, age, participation in social activities, educational level, level of physical activity, and drinking alcohol status, as shown in Table 1. As such, it is important to exclude the effects of these confounding factors. The Cox proportional risk model analysis results are presented in Table 6. Age ≥75 years, men (HR: 1.903, 95% CI: 1.468–2.466), never participating in community activities, physical activity other than high intensity, and frailty were risk factors influencing the incidence of infectious diseases. Corrected for these factors, frailty status continued to have a significant effect on the incidence of communicable disease in frail older adults (HR: 1.50, 95% CI: 1.14–1.97).

Table 6. Results of Cox proportional risk model analysis affecting the incidence of infectious diseases in frail older adults.

factor	*P*	HR	95%CI HR
group			
control	Ref		

frailty	.004	1.50	1.14-1.97
Age			
65-	Ref		
75-	<.001	1.97	1.50-2.60
85-	.03	1.75	1.06-2.90
Gender			
Women	Ref		
Men	<.001	1.92	1.48-2.48
Participation in community activities			
never	Ref		
frequent	.02	0.65	0.46-0.93
ocassional	.62	1.11	0.73-1.70
Physical activity level			
High intensity	Ref		
Low intensity	.22	1.31	0.85-2.00
Medium intensity	.002	1.74	1.23-2.47

Sensitivity Analyses

Sensitivity analyses assessing the robustness of our findings are described in Table 7. When infected with the hepatitis B and C viruses, patients do not experience symptoms immediately, but rather go through a period of incubation before developing the disease. Hepatitis B carriers have an indeterminate amount of time to develop symptoms and may not even develop the disease. Hepatitis C has an insidious onset, and the initial symptoms are not obvious. So there may be a discrepancy between the time of onset of the disease as detected and the actual time of onset of the disease. In addition, among respiratory tract transmitted diseases, tuberculosis is a chronic infectious disease. Its early stage often does not have very special symptoms. Patients only have a slight cough or cough sputum, so this symptom is easily ignored by patients and they do not go to see a doctor. It usually has a longer incubation period, sometimes several years or even lifelong. Therefore, the actual onset time of these three types of patients is difficult to determine. In order to exclude this part of the impact, we removed the data of these three types of patients and re-analyzed the impact of infectious diseases with different transmission routes. The results did not differ from the previous results.

Table 7 Results of Cox proportional risk model analysis of infectious diseases affecting the onset of infectious diseases in frail older adults (excluding hepatitis B and C and tuberculosis).

factor	*P*	HR	95%CI HR
Group			
Control	ref		
Frailty	<.001	1.83	1.36-2.46
Age			

65-	ref		
75-	<.001	1.98	1.46-2.69
85-	.009	1.98	1.18-3.30
Gender			
Women	ref		
Men	<.001	2.05	1.54-2.72
Physical activity level			
High intensity	ref		
Low intensity	.13	1.45	0.90-2.32
Medium intensity	<.001	1.95	1.32-2.88

Figure1 shows survival curves of frailty on infectious diseases in general, frailty on respiratory-transmitted diseases(Figure2), frailty on gastrointestinal-transmitted diseases(Figure3), and frailty on blood-borne diseases, sexually transmitted and contact-transmitted diseases (Figure4). It can be seen that frailty has less of an effect on gastrointestinal-transmitted, blood-borne, sexually transmitted, and contact-transmitted diseases, while it has some effect on respiratory-transmitted diseases.

Discussion

Principal Findings

Our study demonstrated that frailty is associated with an increased risk of infection. This association was discovered in a longitudinal analysis of community-dwelling elderly who either became frail or remained healthy. The robustness of our results was confirmed with various sensitivity analyses.

Overall, the risk of infection increased for frail elderly. Other factors included age, level of physical activity, and participation in community activities.

Immunosenescence is associated with increased susceptibility to infectious pathogens and poor vaccine responses in older adults[16]. Aging of the immune system leads to a low-level chronic systemic inflammatory state that is basically inactive—called “inflammatory ageing”[17]. It was suggested that so-called “inflamm-aging” may slowly damage one or several organs, leading to an increased risk of age- related chronic diseases and frailty[18]. There is poor immune system activity and long-standing inflammation among frail elderly compared with the general population[19]. In addition, frailty is more prevalent among physically inactive, sedentary older people[20]. Research suggests that regular exercise of adequate intensity strengthens the immune system[21]. Laetitia Gay et al. showed that women have a lower risk of most infectious diseases than men[22]. Moreover,

because frailty is increasingly prevalent in the elderly population, frailty identification should be incorporated in measures to prevent infectious diseases when facing emerging and re-emerging infectious diseases.

In addition, frail elderly had an HR for respiratory tract transmitted diseases of 1.97 (95% CI: 1.44–2.71) compared with healthy elderly. Frailty increases the risk of developing COVID-19 and influenza[11, 23]. The danger of tuberculosis among the elderly increases with sarcopenia and physical inactivity, and sarcopenia is a major component of the frailty syndrome[24, 25]. Previous research on the association between frailty and respiratory tract transmitted diseases has primarily focused on individual diseases. Although our study centers on the category of respiratory tract transmitted diseases, our results are consistent with those of prior research. Our study underscores the need for transmission routes to evaluate the associations of frailty with infectious diseases.

Frail elderly people are more susceptible to gastrointestinal tract transmission diseases compared to the general population. However, we only collected other infectious diarrheal diseases, namely infectious diarrhea other than cholera, dysentery, typhoid, and paratyphoid. It has been noted in the literature that nosocomial norovirus infection usually involves frail elderly patients who may have prolonged symptoms[26]. As we age, the immune system and gut microbiota undergo significant changes in composition and function. These changes are associated with increased susceptibility to infectious diseases and decreased vaccination responses[27]. The dynamic microbial community of the human gastrointestinal tract plays a crucial role in health processes and supports the development and function of the intestinal immune barrier[28]. Furthermore, previous findings suggest that aging-associated microbiota can promote intestinal permeability and inflammation and eventually increase the levels of frailty- related pro-inflammatory cytokines[29, 30] .

HIV-infected patients have a high prevalence of frailty[31]. Research by Jenny Pena Dias et al. showed that sex hormone–binding globulin (SHBG) is higher in patients with HIV (PWH) and hepatitis C virus (HCV), and that SHBG is associated with aging-related conditions such as osteoporosis and frailty in the general population[32]. However, in the present study, we did not find an association between debilitation and blood-borne, sexually transmitted and contact- transmitted diseases, and we speculate that this may be due to the fact that these are the types of diseases for which we collected more cases of viral hepatitis and syphilis, which leads to this result due to the presence of an incubation period in these types of infections and the difficulty in determining the true time of onset of the disease.

Strengths and Limitations

The main strength of our study is its prospective nature. Information on frailty was collected before infection. In addition, we adjusted for transmission routes, which is an important determinant

of the prevention of infectious diseases. Our study has the following limitations. First, we only collected 235 cases with 12 infectious diseases, and these did not cover all types of infectious diseases. Hence, more research is needed to confirm these findings. Second, our assessment of physical activity levels was obtained by self-reports, which may have introduced recall bias.

Conclusion

In summary, our population-based research suggests that frailty increases the risk of infectious diseases in older adults. Thus, identifying the frailty state of older adults can help mitigate the risk and burden of infectious diseases.

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Ya Yang and Kechun Che wrote the manuscript and performed statistical analysis. Ya Yang, Kechun Che, Wenyuan Jing, Xiuping He, Jiacheng Yang, Xinming Tang, Jiayan Deng, Wenya Zhang conceived and designed the study and interpreted the data. Xiaoling Huang, Mingjuan Yin, Congcong Pan critically revised the manuscript. Zewu Zhang and Jindong Ni are the guarantors of this work and approved the final version.

The first two authors contributed equally and was greater.

Conflicts of Interest

None declared

Abbreviations

IRR incidence rate ratio

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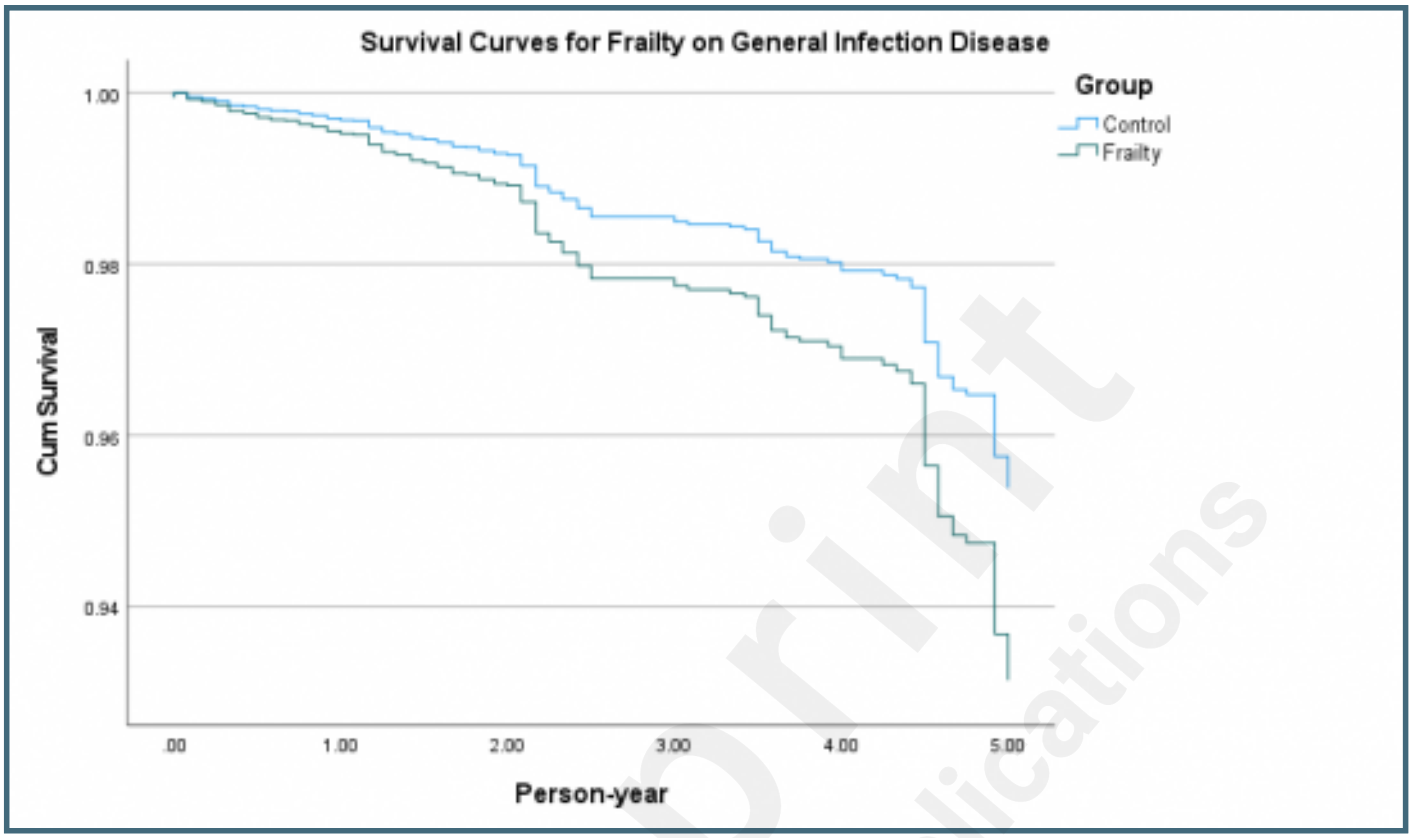
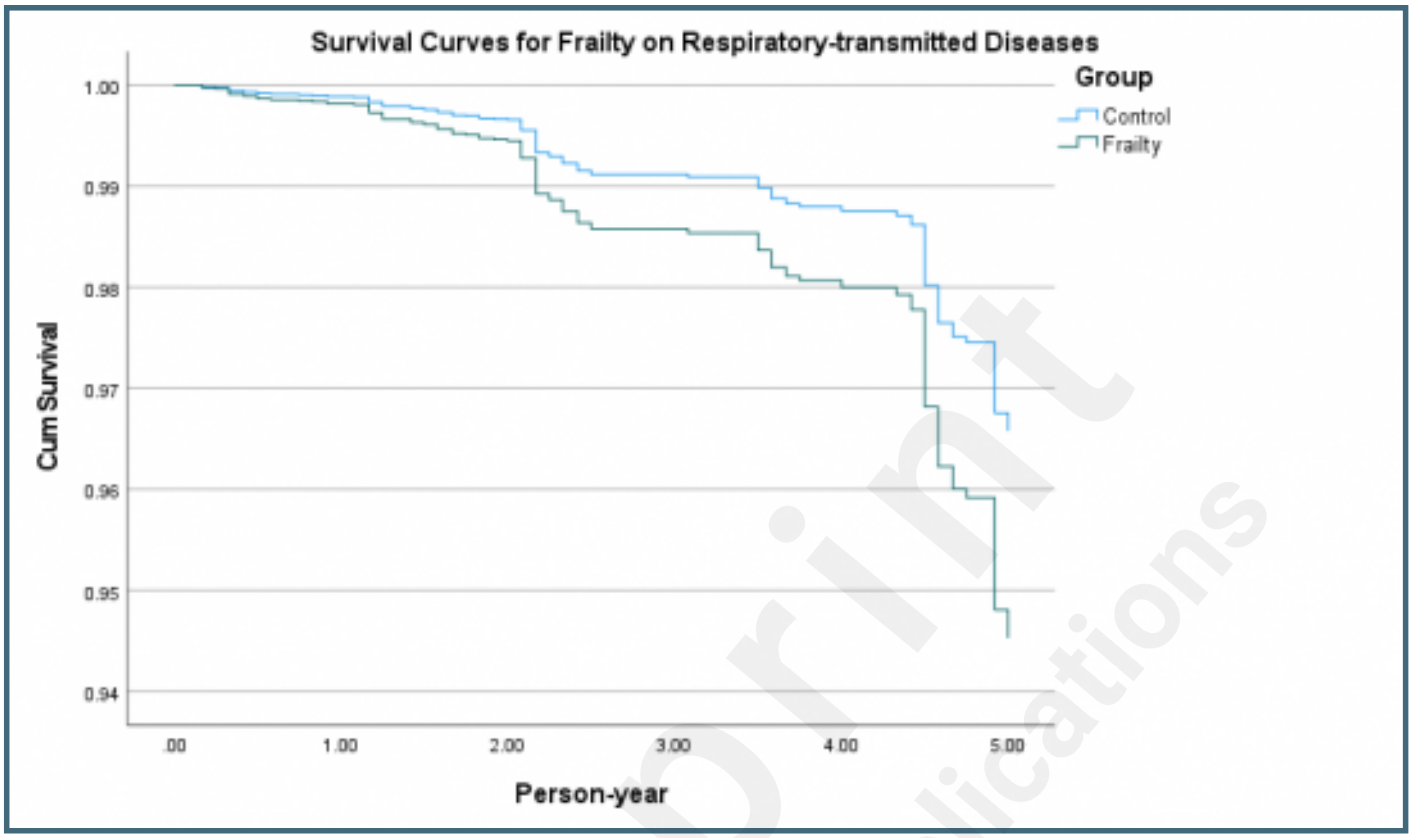
Supplementary Files

Figures

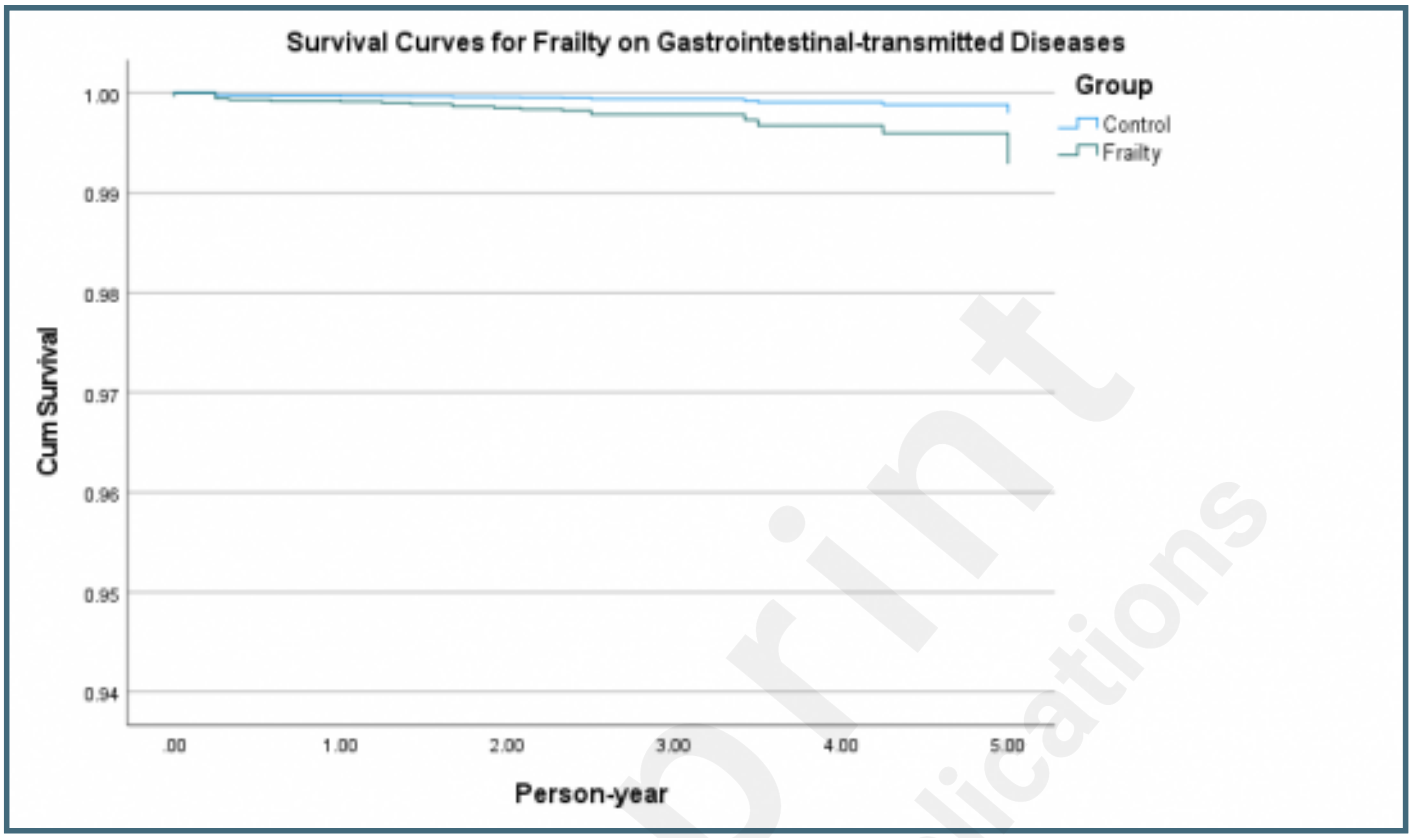
Survival Curves for the frailty on general Infectious diseases.



Survival Curves for the frailty on respiratory-transmitted diseases.



Survival Curves for the frailty on gastrointestinal-transmitted diseases.



Survival Curves for the frailty on blood-borne diseases, and sexually transmitted and contact-transmitted diseases.