

Clinical Characteristics and Comorbidity Patterns Linked to COVID-19 Mortality: Evidence from Yemen

Mohammed A. Awn

DOI: [https://doi.org/10.47372/yjmhr.2026\(15\).2.2](https://doi.org/10.47372/yjmhr.2026(15).2.2)

Abstract

Introduction: The COVID-19 pandemic has presented severe challenges worldwide, especially in conflict-affected and resource-constrained countries like Yemen. Yemen's fragile health system, weakened by ongoing conflict and humanitarian crises, has struggled to respond effectively. This study aimed to assess the clinical characteristics, outcomes, and mortality risk factors among COVID-19 patients admitted to public isolation units during the first pandemic wave across multiple governorates in Yemen.

Methods: A retrospective observational cross-sectional study was conducted using data from 308 laboratory-confirmed COVID-19 patients admitted to isolation units across eight governorates between May and June 2020. Demographic details, comorbidities, clinical presentations, and outcomes (discharge, ongoing treatment, and death) were collected from Ministry of Public Health and Population records and analyzed using SPSS version 23.0. Findings were presented as frequencies and percentages.

Results: Most cases were males (72.7%), with middle-aged adults (45–69 years) comprising the largest group (53.2%). Mortality was notably higher among males (80.3%) and older adults (≥ 70). The most prevalent comorbidities were diabetes mellitus (34.7%) and arterial hypertension (27.6%); both strongly linked to increased mortality. Fever (92.9%), cough (89.3%), and difficulty breathing (87.7%) were the predominant symptoms, with many patients presenting at advanced diseases stages characterized by respiratory complications.

Conclusion: Older age, male sex, and chronic comorbidities, particularly Cardiovascular diseases, Pneumonia and Diabetes Mellitus, are major characteristics linked to poor COVID-19 outcomes in Yemen. These findings highlight the critical need for integrated chronic disease management within emergency health responses. Strengthening primary healthcare services, expanding early case detection, and improving health system resilience are vital to reduce mortality and enhance pandemic preparedness in fragile conflict-affected settings.

Keywords: COVID-19, Yemen, Mortality, Comorbidities, Health System, Conflict, Clinical Outcomes.

Humanitarian Affairs Officer – Coordination Unit, United Nations Office for the Coordination of Humanitarian Affairs (OCHA), Aden

Corresponding Author: Mohammed A. Awn. **Email:** mawn665@gmail.com

الخصائص السريرية وأنماط الأمراض المصاحبة المرتبطة بالوفيات الناجمة عن كوفيد-19: أدلة من اليمن

محمد عبدالباري عون

ملخص الدراسة

المقدمة : لقد شكّلت جائحة كوفيد-19 تحديات كبيرة على مستوى العالم، وخاصة في الدول المتأثرة بالنزاعات والمحدودة الموارد مثل اليمن. يعاني النظام الصحي في اليمن من هشاشة شديدة نتيجة النزاع المستمر والأزمة الإنسانية، مما أعاق الاستجابة الفعالة للجائحة. تهدف هذه الدراسة إلى تقييم الخصائص السريرية، والنتائج، وعوامل خطر الوفيات بين مرضى كوفيد-19 الذين تم قبولهم في وحدات العزل العامة خلال الموجة الأولى للجائحة في عدة محافظات باليمن.

المنهجية: أجريت دراسة مقطع عرضي استرجاعية باستخدام بيانات 308 من مرضى كوفيد-19 المؤكد تشخيصهم مخبرياً والذين تم قبولهم في وحدات العزل في ثماني محافظات بين مايو ويونيو 2020. تم جمع البيانات الديموغرافية، والأمراض المصاحبة، والعلامات السريرية، والنتائج (التمائل للشفاء، العلاج المستمر، الوفاة) من سجلات وزارة الصحة العامة والسكان، وحُللت باستخدام برنامج SPSS الإصدار 23.0. تم عرض النتائج كتواتر ونسب مئوية.

النتائج: شكل الذكور 72.7% من الحالات، وكانت الفئة العمرية 45-69 عامًا هي الأعلى نسبة (53.2%). كان معدل الوفيات أعلى بشكل ملحوظ بين الذكور (80.3% من الوفيات) وكبار السن (أكبر أو يساوي 70 عامًا). كانت الأمراض المصاحبة الأكثر شيوعاً هي داء السكري (34.7%) وارتفاع ضغط الدم الشرياني (27.6%)، وكلاهما مرتبط بشكل قوي بزيادة الوفيات. كانت الحمى (92.9%)، والسعال (89.3%)، وصعوبة التنفس (87.7%) من الأعراض السائدة، مع دخول العديد من المرضى في مراحل متقدمة من المرض مع مضاعفات تنفسية.

الخلاصة: تؤكد الدراسة أن العمر الأكبر، والذكور، والأمراض المزمنة، وخاصة أمراض القلب والأوعية الدموية، والالتهاب الرئوي، ومرض السكري، هي عوامل رئيسية مرتبطة بنتائج سيئة لكوفيد-19 في اليمن. تبرز هذه النتائج الحاجة الملحة لإدماج إدارة الأمراض المزمنة ضمن الاستجابات الصحية الطارئة. إن تعزيز خدمات الرعاية الصحية الأولية، وتوسيع الكشف المبكر عن الحالات، وتحسين مرونة النظام الصحي أمر حيوي لتقليل الوفيات وتعزيز الجاهزية لمواجهة الجوائح في البيئات الهشة المتأثرة بالنزاعات.

كلمات مفتاحية: كوفيد-19، اليمن، الوفيات، الأمراض المصاحبة، النظام الصحي، النزاع، النتائج السريرية.

ضابط الشؤون الإنسانية - وحدة التنسيق مكتب الأمم المتحدة لتنسيق الشؤون الإنسانية (أوتشا)

Introduction

Since the emergence of COVID-19 in late 2019, the virus has led to significant global health challenges. As of 2023, over 80 million people have been infected globally and resulted in more than one million deaths across more than 190 countries worldwide [1]. The virus spreads primarily through airborne respiratory droplets and is transmissible by both symptomatic and asymptomatic individuals [2,3].

In the context of the protracted conflict in Yemen, the country finds itself at a critical juncture at the end of 2023. Nine years since the escalation of the current crisis and more than a year after the expiry of the truce between the parties, the prospect of a peaceful resolution remains in sight. However, the conflict has placed considerable strain on basic services and hosting communities, with reportedly 50% of hospitals either fully or partially non-functional due to war-related damage [4].

Yemen is considered to be at high risk for disease outbreaks, with devastating epidemics of cholera, measles, diphtheria, dengue fever, and polio in recent years [5,6]. Key contributing factors include severely limited public health infrastructure and services, water scarcity, and growing levels of vaccine hesitancy and refusal. In 2023, the country experienced a resurgence of vaccine-preventable diseases, including cholera, acute watery diarrhoea, measles, polio, pertussis, and diphtheria, with unvaccinated children comprising a significant proportion of those affected. Across Yemen, an estimated 70% of children

aged three years have not received a full course of recommended vaccinations [7].

Yemen's first confirmed case of COVID-19 was officially reported by the Ministry of Public Health and Population (MoPHP) on 10 April 2020 [8]. While available data suggest a peak in mortality during the early phase of the pandemic, the lack of robust surveillance in some parts of the country has hindered accurate estimations of death trends [9]. Clinically, COVID-19 in Yemen presents with nonspecific symptoms, most commonly fever, cough, fatigue, and myalgia [10]. Among laboratory-confirmed cases, individuals with comorbidities had poorer outcomes, and disease severity increased with the number of pre-existing conditions [11]. During the COVID-19 pandemic, Yemen's conditions closely mirrored those of an active conflict setting. The health system was overwhelmed, relying on makeshift field hospitals, strict triage to ration limited care, and daily mortality reporting that far exceeded peacetime capacity. Evidence from neighbouring countries and global contexts documented similar pressures on health services and adverse outcomes, highlighting shared systemic vulnerabilities and reinforcing the urgent need to invest in resilient and shock-responsive health systems [12,13]. Thus, the objective of this study is to assess the clinical characteristics, outcomes, and mortality associated factors among COVID-19 patients admitted to public isolation units during the first wave of the pandemic in Yemen.

Methods

Study design and setting

This retrospective cross-sectional study analyzed data from 308 COVID-19 patients admitted to isolation units across eight governorates (Aden, Taiz, Lahj, Abyan, Al Dhalea, Shabwah, Al Maharah, Marib) between May and June 2020.

Target population

Patients admitted to the isolation units in the selected eight governorates within May-June 2020. The study excluded COVID-19 cases which were admitted to the private sector hospitals.

Data collection

Data were collected from verified medical records maintained by the MoPHP. Data collected included demographic information, comorbidities (arterial hypertension, diabetes, cardiovascular, lung, liver, and kidney diseases), presenting symptoms, and clinical outcomes (intensive care unit-ICU admission, recovery, death) extracted from surveillance sheets and ICUs admission forms used uniformly across MoPHP-supported public isolation units. These forms included predefined variables on demographics, comorbidities, clinical presentation, and outcomes, ensuring consistency and comparability across participating facilities. Records were reviewed for completeness during data cleaning, and cases with missing or inconsistent information on key variables (age, sex, laboratory confirmation, or clinical outcome) were excluded prior to analysis.

Statistical analysis

Data were processed using SPSS version 23. Descriptive statistics were used to analyse demographic distributions and morbidity patterns. Categorical variables were presented in frequency and percentage while quantitative variables were presented as means and standard deviations.

Ethical consideration

Permission was given from the MoPHP, Curative Health Care Sector based on an official letter from the Yemeni Council of Medical Specialization-Aden. Only anonymized, routine data were used; thus, informed consent was not required.

Results

The final analytic sample comprised 308 laboratory-confirmed COVID-19 cases with sufficiently complete records. The analysis reveals a significant age-related trend. The mean age was 57.0 years $\pm$ 16.1 years. The majority of patients (53.2%) aged between 45 and <70 years, while an additional 11.7% aged 70 years or older. Together, these groups accounted for nearly two-thirds (64.9%) of all admissions. In contrast, children under 15 years constituted only 1.3% of cases, and the 15 - <30 age group made up 11.0%.

A striking sex disparity was observed among the admitted cases. Males represented 72.7% of all patients. On the other hand, geographic distribution of cases was also notably

uneven. Three governorates—Aden (26.9%), Taiz (26.6%), and Shabwa (20.5%)—together accounted for approximately 74.0% of all reported

admissions. In contrast, some governorates such as Abyan and Al Maharah reported only two cases each (0.6%) as shown in Table 1.

Table 1: Characteristic of Admitted Studied COVID-19 Cases (n=308)

Characteristics	No.	%
Age groups in years		
0 - <15	04	1.3
15 - <30	34	11.0
30 - <45	70	22.7
45 - <70	164	53.2
≥70	36	11.7
Mean age	57±16.1	
Sex		
Male	224	72.7
Female	84	27.3
Governorate		
Aden	83	26.9
Taizz	82	26.6
Shabwa	63	20.5
Lahj	47	15.3
Al Dhale'e	22	7.1
Marib	07	2.3
Abyan	02	0.6
Al Maharah	02	0.6

In Table 2, symptoms profile among admitted COVID-19 patients reveals that the vast majority presented with classic clinical features of the disease. High temperature was reported in 92.9% of cases, making it the most common symptom. Cough and difficulty in breathing were also highly prevalent, affecting 89.3% of patients. Muscle and joint pain were present in 82.5%, and sore throat in 78.2% of cases. Shortness of breath, although slightly less frequent, still occurred in more than half of the patients (59.1%).

In terms of comorbidities, a significant portion of the admitted patients had underlying health conditions. Diabetes mellitus was the most commonly reported comorbidity (34.7%). Arterial hypertension followed at 27.6%, while Pneumonia was identified in 25.3% of patients. Cardiovascular disease was documented in 24.0% of cases. Kidney disease affected 24.0%, while Chronic lung disease and liver disease were each present in 19.8% of patients. Table 2 also shows that, around the half (48.7%) of admitted COVID-19 cases were still under treatment at the time of data extraction, 29.8% discharged and 23.5% died.

Table 2: Distribution of Studied Admitted COVID-19 Cases by Clinical Manifestation, Comorbidities and Outcomes (n=308)

Characteristics	No.	%
Clinical Manifestation		
High temperature	286	92.9
Cough	270	89.3
Difficulty in breathing	270	89.3
Muscle and joint pain	245	82.2
Sore throat	241	78.2
Shortness of breath	182	59.1
Comorbidities		
Diabetes Mellitus	107	34.7
Arterial Hypertension	85	27.6
Pneumonia	78	25.3
Cardiovascular Disease	74	24.0
Kidney Disease	74	24.0
Chronic Lung Disease	61	19.8
Liver Diseases	61	19.8
Outcomes		
Under treatment	147	48.7
Discharged	90	29.8
Dead	71	23.5

The analysis of COVID-19 outcomes by age and gender among admitted cases reveals clear disparities. Age-wise, the highest death percentage was observed in patients aged ≥ 70 (30.6%), followed by the 45–<70 years group at 26.2%. Death declined sharply in younger groups, with only 5.9% in the 15–<30 years group and no deaths reported in children under 15 years. Younger patients,

particularly those aged 15–<30 years, had the highest discharge rate (44.1%). Notably, a large proportion of cases across all age groups remain under treatment, with the highest ongoing care seen in the youngest group (0–<15 years) at 75%. Regarding gender, males had higher percentage of deaths (25.5%) compared to females (16.7%) as illustrated in Table 3.

Table 3: Distribution of Studied Admitted COVID-19 Cases Outcomes by Age Group and Sex (n=308)

Characteristics	Outcome*					
	Under treatment (n=147)		Discharged (n=90)		Dead (n=71)	
	No.	%	No.	%	No.	%
Age group						
≥ 70 (n=36)	16	44.4	9	25.0	11	30.6
45 – <70 (n=164)	75	45.7	46	28.0	43	26.2
30 – <45 (n=70)	36	51.4	19	27.1	15	21.4
15 – <30 (n=34)	17	50.0	15	44.1	2	5.9
0 – <15 (n=04)	3	75.0	1	25.0	0	0.0
Sex						
Male (n=224)	106	47.3	61	27.2	57	25.5
Female (n=84)	41	48.8	29	34.5	14	16.7

* Percentages taken from rows total.

Among admitted COVID-19 cases with comorbidities, 35.1%, 34.6%, 33.6% and 32.8% of COVID-19 cases with cardiovascular diseases, Pneumonia, Diabetes Mellitus, and

chronic lung diseases respectively had died, while 30.6% of those cases with arterial hypertension had died as shown in Table 4.

Table 4: Frequency of Deaths among Studied Admitted COVID-19 Cases with Comorbidities (n=71)

Comorbidities	Died admitted COVID-19 cases (n=71)	
	No.	%
Cardiovascular Diseases (n=74)	26	35.1
Pneumonia (n=78)	27	34.6
Diabetes Mellitus (n=107)	36	33.6
Chronic Lung Diseases (n=61)	20	32.8
Kidney Diseases (n=74)	23	31.1
Liver Diseases (n=61)	19	31.1
Arterial Hypertension (n=85)	26	30.6

Discussion

This study provides multi-governorate evidence on the clinical characteristics, comorbidity patterns, and mortality outcomes among hospitalized COVID-19 patients in Yemen during the first wave of the pandemic. The findings highlight a disproportionate burden of severe disease and mortality among older adults and males, particularly those with underlying non-communicable diseases, reflecting both global epidemiological trends and context-specific vulnerabilities within Yemen's fragile health system.

The marked predominance of male patients (72.7%) and higher mortality among men is consistent with international evidence indicating greater susceptibility to severe COVID-19 outcomes among males [14,15]. Biological factors, including sex-based immunological differences, as well as behavioral and occupational exposure patterns, have been proposed as contributing

mechanisms [15]. In Yemen, these disparities may be further amplified by gendered social roles, higher mobility among men, and differential health-seeking behaviors, while women's access to formal healthcare services remains constrained by structural and cultural barriers [16]. Consequently, female cases may be underrepresented in facility-based data, potentially masking disease burden among women.

Age emerged as a prominent factor associated with death, with patients aged ≥ 70 years experiencing the highest death rates, followed by those aged 45–<70 years. This pattern aligns closely with global analyses demonstrating a steep age gradient in COVID-19 severity and fatality [17,18]. The absence of deaths among children and the low mortality observed in younger adults are consistent with evidence from large cohort and modeling studies indicating reduced risk of severe

outcomes in younger populations [18]. However, in Yemen's context, delayed presentation to care and limited early detection may contribute to higher severity at admission among older patients, exacerbating mortality risk. The clinical presentation observed in this study widely reported global symptom profiles, with fever, cough, and difficulty in breathing being the most prevalent manifestations [18]. The very high proportion of patients presenting with respiratory distress underscores the advanced stage of disease at the time of admission, reflecting delays in care-seeking and limited community-level surveillance during the early phase of the pandemic [19]. Such late presentations likely contributed to the elevated mortality observed in this study.

Comorbidities played a central role in shaping disease outcomes. Diabetes mellitus and arterial hypertension were the most prevalent underlying conditions, while cardiovascular disease and pneumonia were most strongly associated with mortality. These findings are consistent with large international cohort studies and meta-analyses demonstrating that cardiovascular disease, diabetes, and hypertension significantly increase the risk of severe COVID-19 and death [14,18]. The high prevalence of pneumonia among admitted patients further reflects advanced disease progression and aligns with evidence linking secondary respiratory complications to poor outcomes [20]. On the other hand, kidney and chronic lung diseases also showed substantial mortality proportions, corroborating global evidence of their role in complicating clinical management and increasing fatality risk [18].

In Yemen, the interaction between COVID-19 and non-communicable diseases is particularly concerning. Prolonged conflict has disrupted chronic disease management, weakened primary healthcare services, and limited access to essential medications, thereby increasing vulnerability among patients with pre-existing conditions [19]. The findings suggest that COVID-19 mortality in Yemen cannot be understood in isolation from the broader health system context, where fragmented care pathways and reduced preventive services likely intensified disease severity and adverse outcomes.

Geographic clustering of cases in urban governorates such as Aden, Taizz, and Shabwa likely reflects both higher population density and better availability of isolation units and reporting mechanisms, rather than true differences in transmission alone. This uneven distribution highlights persistent inequities in access to COVID-19 diagnostic and treatment services across governorates, a challenge also documented in other fragile and conflict-affected settings [19].

Overall, the study situates Yemen's COVID-19 experience within global patterns of age-, sex-, and comorbidity-related risk, while underscoring the compounding effects of conflict, health system fragility, and delayed care. These findings reinforce the importance of integrating non-communicable disease management, early case detection, and equitable access to care into pandemic preparedness and response strategies in fragile settings.

Limitations

This study relied on routinely collected surveillance and medical record data, which may be subjected to incomplete or inconsistent documentation, particularly within a protracted conflict-affected health system. Although standardized MoPHP reporting tools were used across all included public isolation units and records were screened for completeness prior to analysis, some degree of residual missingness or reporting bias cannot be fully excluded.

In addition, the analysis was limited to patients admitted to public isolation units and did not capture cases managed in private facilities or within the community, potentially underestimating the true burden of COVID-19 and related mortality. Clinical data were restricted to variables routinely recorded in surveillance forms, limiting the assessment of laboratory parameters, treatment modalities, and temporal disease progression.

Finally, the retrospective and descriptive nature of the study precludes causal inference, and findings should be interpreted within the context of the first wave of the pandemic, when testing capacity, clinical protocols, and health system preparedness were rapidly evolving. Despite these limitations, the study provides valuable multi-governorate evidence on COVID-19 clinical characteristics and mortality risk factors in a highly fragile and under-researched setting.

Conclusion

This study demonstrates that COVID-19 had a disproportionate impact on males and older adults with pre-existing conditions such as diabetes, hypertension, and cardiovascular disease in Yemen. Late hospital admissions with severe symptoms like pneumonia suggest delays in care-seeking and limited early detection. Strengthening provider training, community surveillance, and early intervention pathways is crucial to improve timely diagnosis and treatment. Ultimately, addressing Yemen's structural health system weaknesses—particularly in preventive care, chronic disease management, and emergency preparedness—is essential to enhance resilience against future health crises.

References

1. Johns Hopkins University. COVID-19 dashboard by the Center for Systems Science and Engineering (CSSE) [Internet]. Baltimore: Johns Hopkins University; 2023 [cited 2025 Jan 22]. Available from: <https://coronavirus.jhu.edu/map.html>
2. Hossain MM, Sultana A, Purohit N. Mental health outcomes of quarantine and isolation for infection prevention: a systematic umbrella review of the global evidence. *Epidemiol Health*. 2020;42:e2020038.
3. Harmooshi NN, Shirbandi K, Rahim F. Environmental concern regarding the effect of humidity and temperature on 2019-nCoV survival: fact or

- fiction. *Environ Sci Pollut Res Int.* 2020;27(36):36027–36036.
4. United Nations Office for the Coordination of Humanitarian Affairs. Yemen humanitarian needs overview 2023 [Internet]. New York: OCHA; 2023 [cited 2025 Dec 10]. Available from: <https://reliefweb.int/report/yemen/yemen-humanitarian-needs-overview-2023>
5. INFORM Risk Index. Yemen country profile 2023 [Internet]. Brussels: European Commission Joint Research Centre; 2023 [cited 2025 Jul 16]. Available from: <https://drmkc.jrc.ec.europa.eu/inform-index/INFORM-Risk/Country-Profile>
6. World Health Organization. Yemen: disease outbreaks situation report [Internet]. Geneva: WHO; 2023 [cited 2025 May 04]. Available from: <https://www.who.int/emergencies/disease-outbreak-news/item/2023-DON-Yemen>
7. UNICEF, Central Statistical Organization (CSO). Yemen multiple indicator cluster survey 2023: final report [Internet]. New York: UNICEF; 2023 [cited 2025 Aug 02]. Available from: <https://mics.unicef.org/surveys>
8. Ministry of Public Health and Population. COVID-19 updates [press release]. Aden: MoPHP; 2020 Apr 10.
9. Checchi F, Warsame A, Treacy-Wong V, Polonsky J, van Ommeren M, Prudhon C. Public health information in crisis-affected populations: a review of methods and their use for advocacy and action. *Lancet.* 2021;397(10288): 1436–1446.
10. World Health Organization. COVID-19 Yemen situation report 2021 [Internet]. Geneva: WHO; 2021 [cited 2023 Dec 20]. Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>
11. Al-Aghbari N, Al-Dheeb N, Al-Moyed KA, Al-Serouri A, Al-Kohlani A, Al-Dailami A, *et al.* Epidemiological and clinical characteristics of COVID-19 cases in Yemen: a descriptive study. *East Mediterr Health J.* 2021; 27(10):1010–1016.
12. Filip R, Gheorghita-Puscaselu R, Anchidin-Norocel L, Dimian M, Savage WK. Global challenges to public health care systems during the COVID-19 pandemic: a review of pandemic measures and problems. *J Pers Med.* 2022;12(8):1295.
13. Kotiso M, Qirbi N, Al-Shabi K, Vuolo E, Al-Waleedi A, Naiene J, *et al.* Impact of the COVID-19 pandemic on the utilisation of health services at public hospitals in Yemen: a retrospective comparative study. *BMJ Open.* 2022; 12(1):e047868.
14. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al.* Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020; 395(10229):1054–1062.
15. Bwire GM. Coronavirus: why men are more vulnerable to COVID-19 than women? *SN Compr Clin Med.* 2020;2(7):874–876.

16. United Nations Population Fund. Women and girls left behind: the gendered impact of COVID-19 in Yemen [Internet]. Sana'a: UNFPA; 2021 [cited 2024 Feb 02]. Available from: <https://yemen.unfpa.org/>
17. Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. *Lancet Infect Dis*. 2020;20(6):669–677.
18. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al. Comorbidity and its impact on 1,590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J*. 2020;55(5):2000547.
19. Al-Awlaqi S, Dureab F, Annuzaili D, Al-Dheeb N. COVID-19 in Yemen: preparedness measures in a fragile state. *Lancet Public Health*. 2020;5(6):e311.
20. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497–506.