Systematically mapping clinical features of infections with classical endemic human coronaviruses

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Dear editor,

The classical endemic human coronaviruses including HKU1, OC43, NL63 and 229E are widely circulating among the global population. However, research on these coronaviruses has been largely neglected, until the recent outbreak of SARS-CoV-2 that caused COVID-19 pandemic. Emerging evidence indicates cross-reactive immunity towards SARS-CoV-2 by pre-exposure of endemic coronaviruses, which may induce possible protective effects but could also interfere with serological diagnosis of COVID-19 [1]. Therefore, several recent studies have investigated the prevalence of these endemic coronaviruses [2-4]. In line with these studies, Cummings et al [5] found that 8% of healthcare personnel were infected with endemic coronavirus, and they further investigated risk factors of the infection. However, little efforts have been dedicated to understand their clinical features. Such knowledge is essentially required for assessing the burden of endemic coronavirus infection *per se*, but also for better understanding the implications in COVID-19 pandemic.

In this study, we performed a systematic review and meta-analysis to comprehensively characterize the epidemiology and clinical features of endemic coronavirus infection (supplementary data). From 3225 searched records, we identified 157 eligible studies originated from 44 countries/territories across six continents. Among the reported 282162 outpatient clinic or hospitalized patients with respiratory symptoms, OC43 was estimated as the most prevalent genotype (2.40%, 95% CI 2.15-2.66%, I^2=95%), followed by NL63 (1.60%, 95% CI 1.39-1.82%, I^2= 95%), HKU1 (1.04%, 95% CI 0.85-1.25%, I^2= 94%) and 229E (0.97%, 95% CI 0.82-1.15%, I^2= 95%) (Figure 1A, supplementary data). Interestingly, the young children group with 0-9 years

old has the highest infection rate of 4.71% (95% CI 3.89-5.60%; I^2=94%), as compared to 0.94% and 2.35% in two older age groups (Figure 1B, supplementary data). This appears in line with the findings of Cummings et al [5] that younger healthcare personnel, those who saw pediatric patients and those with household members under the age of five are at increased risk of infection.

In total, 18 types of clinical symptoms and features have been identified among endemic coronavirus confirmed patients by pooling all the studies irrespective of the genotypes or possible co-infection with multiple genotypes. Fever, cough, rhinorrhea, sore throat and headache commonly occurred in over half of the confirmed patients. Diarrhea was reported in about 5% of patients. Unexpectedly, over 25% patients developed pneumonia potentially resulting in serious complications, although the severity of pneumonia was not specified in these studies (Figure 1C). We further stratified patients with mono-infection of 229E, HKU1, NL63 or OC43, and characterized their clinical symptoms and features respectively (Figure 1D). Strikingly, pneumonia was reported in over 40% patients with NL63 or OC43 infection, although the included patient number is small (supplementary data).

In summary, this study comprehensively characterized the clinical features of endemic coronavirus infection. Despite the intrinsic limitations of retrospective meta-analysis with potential selection and publication bias, our findings suggest that endemic coronavirus can impose substantial clinical burden in a subset of patients, which deserves more attention.

NOTES

Authors contributions

P.L., M.P.P., Z.M. and Q.P. conceived the idea and interpreted data. P.L., A.I. and Q.P. conducted data analysis. P.L. wrote the manuscript. Q.P. critically revised the manuscript.

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Conflict of interest

All the authors declare that they have no conflict of interest.

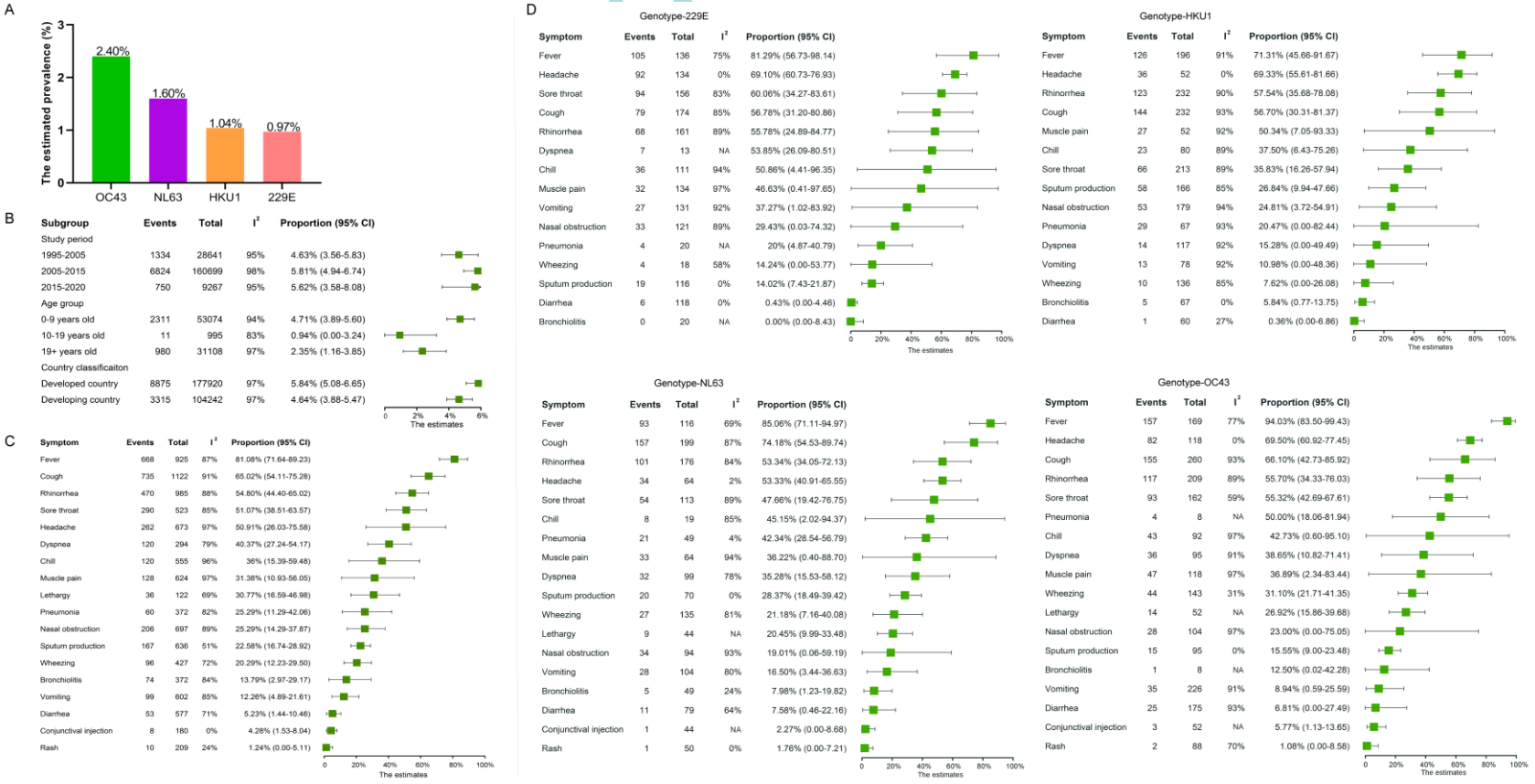
References

1. Grifoni A, Weiskopf D, Ramirez SI, et al. Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals. Cell **2020**; 181(7): 1489-501 e15.
2. Li P, Liu J, Ma Z, Bramer WM, Peppelenbosch MP, Pan Q. Estimating Global Epidemiology of Low-Pathogenic Human Coronaviruses in Relation to the COVID-19 Context. J Infect Dis **2020**; 222(4): 695-6.
3. Nickbakhsh S, Ho A, Marques DFP, McMenamin J, Gunson RN, Murcia PR. Epidemiology of Seasonal Coronaviruses: Establishing the Context for the Emergence of Coronavirus Disease 2019. J Infect Dis **2020**; 222(1): 17-25.
4. Monto AS, DeJonge PM, Callear AP, et al. Coronavirus Occurrence and Transmission Over 8 Years in the HIVE Cohort of Households in Michigan. J Infect Dis **2020**; 222(1): 9-16.
5. Cummings DAT, Radonovich LJ, Gorse GJ, et al. Risk Factors for Healthcare Personnel Infection with Endemic Coronaviruses (HKU1, OC43, NL63, 229E): Results from the Respiratory Protection Effectiveness Clinical Trial (ResPECT). Clin Infect Dis **2020**.

Figure legend

Figure 1. (A) The estimated global prevalence of four endemic coronaviruses including OC43, NL63, HKU1 and 229E. (B) Forest plot of subgroups. (Note: country classification is based on development levels). (C) Forest plot of overall clinical characteristics in endemic coronavirus confirmed patients. (D) Forest plot of clinical characteristics in patients with mono-infection of an individual genotype of endemic coronavirus.

Figure 1


A
The estimated prevalence (%)
2.40%
1.60%
1.04%
0.97%
OC43
NL63
HKU1
229E
B
Subgroup Events Total I² Proportion (95% CI)
Study period
1995-2005 1334 28641 95% 4.63% (3.56-5.83)
2005-2015 6824 160699 98% 5.81% (4.94-6.74)
2015-2020 750 9267 95% 5.62% (3.58-8.08)
Age group
0-9 years old 2311 53074 94% 4.71% (3.89-5.60)
10-19 years old 11 995 83% 0.94% (0.00-3.24)
19+ years old 980 31108 97% 2.35% (1.16-3.85)
Country classificaiton
Developed country 8875 177920 97% 5.84% (5.08-6.65)
Developing country 3315 104242 97% 4.64% (3.88-5.47)
The estimates
C
Symptom Events Total I² Proportion (95% CI)
Fever 668 925 87% 81.08% (71.64-89.23)
Cough 735 1122 91% 65.02% (54.11-75.28)
Rhinorrhea 470 985 88% 54.80% (44.40-65.02)
Sore throat 290 523 85% 51.07% (38.51-63.57)
Headache 262 673 97% 50.91% (26.03-75.58)
Dyspnea 120 294 79% 40.37% (27.24-54.17)
Chill 120 555 96% 36% (15.39-59.48)
Muscle pain 128 624 97% 31.38% (10.93-56.05)
Lethargy 36 122 69% 30.77% (16.59-46.98)
Pneumonia 60 372 82% 25.29% (11.29-42.06)
Nasal obstruction 206 697 89% 25.29% (14.29-37.87)
Sputum production 167 636 51% 22.58% (16.74-28.92)
Wheezing 96 427 72% 20.29% (12.23-29.50)
Bronchiolitis 74 372 84% 13.79% (2.97-29.17)
Vomiting 99 602 85% 12.26% (4.89-21.61)
Diarrhea 53 577 71% 5.23% (1.44-10.46)
Conjunctival injection 8 180 0% 4.28% (1.53-8.04)
Rash 10 209 24% 1.24% (0.00-5.11)
The estimates
D
Genotype-229E
Symptom Events Total I² Proportion (95% CI)
Fever 105 136 75% 81.29% (56.73-98.14)
Headache 92 134 0% 69.10% (60.73-76.93)
Sore throat 94 156 83% 60.06% (34.27-83.61)
Cough 79 174 85% 56.78% (31.20-80.86)
Rhinorrhea 68 161 89% 55.78% (24.89-84.77)
Dyspnea 7 13 NA 53.85% (26.09-80.51)
Chill 36 111 94% 50.86% (4.41-96.35)
Muscle pain 32 134 97% 46.63% (0.41-97.65)
Vomiting 27 131 92% 37.27% (1.02-83.92)
Nasal obstruction 33 121 89% 29.43% (0.03-74.32)
Pneumonia 4 20 NA 20% (4.87-40.79)
Wheezing 4 18 58% 14.24% (0.00-53.77)
Sputum production 19 116 0% 14.02% (7.43-21.87)
Diarrhea 6 118 0% 0.43% (0.00-4.46)
Bronchiolitis 0 20 NA 0.00% (0.00-8.43)
The estimates
Genotype-HKU1
Symptom Events Total I² Proportion (95% CI)
Fever 126 196 91% 71.31% (45.66-91.67)
Headache 36 52 0% 69.33% (55.61-81.66)
Rhinorrhea 123 232 90% 57.54% (35.68-78.08)
Cough 144 232 93% 56.70% (30.31-81.37)
Muscle pain 27 52 92% 50.34% (7.05-93.33)
Chill 23 80 89% 37.50% (6.43-75.26)
Sore throat 66 213 89% 35.83% (16.26-57.94)
Sputum production 58 166 85% 26.84% (9.94-47.66)
Nasal obstruction 53 179 94% 24.81% (3.72-54.91)
Pneumonia 29 67 93% 20.47% (0.00-82.44)
Dyspnea 14 117 92% 15.28% (0.00-49.49)
Vomiting 13 78 92% 10.98% (0.00-48.36)
Wheezing 10 136 85% 7.62% (0.00-26.08)
Bronchiolitis 5 67 0% 5.84% (0.77-13.75)
Diarrhea 1 60 27% 0.36% (0.00-6.86)
The estimates
Genotype-NL63
Symptom Events Total I² Proportion (95% CI)
Fever 93 116 69% 85.06% (71.11-94.97)
Cough 157 199 87% 74.18% (54.53-89.74)
Rhinorrhea 101 176 84% 53.34% (34.05-72.13)
Headache 34 64 2% 53.33% (40.91-65.55)
Sore throat 54 113 89% 47.66% (19.42-76.75)
Chill 8 19 85% 45.15% (2.02-94.37)
Pneumonia 21 49 4% 42.34% (28.54-56.79)
Muscle pain 33 64 94% 36.22% (0.40-88.70)
Dyspnea 32 99 78% 35.28% (15.53-58.12)
Sputum production 20 70 0% 28.37% (18.49-39.42)
Wheezing 27 135 81% 21.18% (7.16-40.08)
Lethargy 9 44 NA 20.45% (9.99-33.48)
Nasal obstruction 34 94 93% 19.01% (0.06-59.19)
Vomiting 28 104 80% 16.50% (3.44-36.63)
Bronchiolitis 5 49 24% 7.98% (1.23-19.82)
Diarrhea 11 79 64% 7.58% (0.46-22.16)
Conjunctival injection 1 44 NA 2.27% (0.00-8.68)
Rash 1 50 0% 1.76% (0.00-7.21)
The estimates
Genotype-OC43
Symptom Events Total I² Proportion (95% CI)
Fever 157 169 77% 94.03% (83.50-99.43)
Headache 82 118 0% 69.50% (60.92-77.45)
Cough 155 260 93% 66.10% (42.73-85.92)
Rhinorrhea 117 209 89% 55.70% (34.33-76.03)
Sore throat 93 162 59% 55.32% (42.69-67.61)
Pneumonia 4 8 NA 50.00% (18.06-81.94)
Chill 43 92 97% 42.73% (0.60-95.10)
Dyspnea 36 95 91% 38.65% (10.82-71.41)
Muscle pain 47 118 97% 36.89% (2.34-83.44)
Wheezing 44 143 31% 31.10% (21.71-41.35)
Lethargy 14 52 NA 26.92% (15.86-39.68)
Nasal obstruction 28 104 97% 23.00% (0.00-75.05)
Sputum production 15 95 0% 15.55% (9.00-23.48)
Bronchiolitis 1 8 NA 12.50% (0.02-42.28)
Vomiting 35 226 91% 8.94% (0.59-25.59)
Diarrhea 25 175 93% 6.81% (0.00-27.49)
Conjunctival injection 3 52 NA 5.77% (1.13-13.65)
Rash 2 88 70% 1.08% (0.00-8.58)
The estimates