COVID-19 and COPD

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COPD patients have increased risk of severe pneumonia and poor outcomes when they develop COVID-19. This may be related to poor underlying lung reserves or increased expression of ACE-2 receptor in small airways. https://bit.ly/37dSB8l

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Is COPD a risk factor for COVID-19?

As of 11 July, 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for the coronavirus disease 2019 (COVID-19) pandemic has infected over 12.7 million people around the world and caused more than 560,000 deaths [1]. Given the devastating impact that COVID-19 can have on the lung, it is natural to fear for patients with underlying COPD. Estimating their excess risk for contracting COVID-19 and, in particular, its more severe respiratory manifestations has been a challenging exercise in this pandemic for various reasons. First, the reporting on cases has concentrated on hospitalised and intensive care unit (ICU) patients, rather than on mild, outpatient cases. This is in part also due to the variability in testing strategies across the world, where some nations with stricter testing requirements and scarce testing resources have focused on testing only those requiring hospitalisation. We have also not yet quantified how many COPD patients might have chosen never to present to a hospital in this pandemic, only to subsequently appear in the statistics for excess mortality during this time [2, 3]. Second, the underestimation of COPD in the general population is a problem that predates the COVID-19 era [4–6] and one that is likely to be exacerbated in overburdened hospitals where the precise ascertainment of comorbidities may be overlooked and spirometry cannot be performed. Moreover, how the diagnosis of COPD has been adjudicated in these studies has not been clearly delineated, possibly giving rise to variability in prevalence across the world.

Due to the earlier time course of infections there, our most thorough snapshot of COPD in COVID-19 is from China, where the background rate of COPD is 13.6% in adults aged >40 years [7]. The vast majority of these studies have centred on hospitalised patients, with only one to date including both hospitalised patients and outpatients (of which only 1.1% carried a diagnosis of COPD [8]) and one considering asymptomatic patients (of which only 1.6% had COPD [9]). For cohorts in China reporting on hospitalised patients, the prevalence of COPD has ranged from 0 to 10% (table 1) [10–41]. As data from other nations have trickled in, the figures for COPD amongst hospitalised COVID-19 patients appear to be similar, with estimates in New York City ranging from 2.4 to 14% [42–45] and in Italy ranging from 5.6 to 9.2% [46–48]. Data from ICU-only cohorts, however, have been more variable. One cohort in Italy totalling 1591 ICU patients [49] and one in Seattle with 24 ICU patients noted COPD rates of 4% in each [50]. Much higher prevalence has been reported in a Spanish ICU of 48 patients, of which 38% had COPD [51], and in another Seattle ICU of

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TABLE 1 COPD and smoking prevalence in coronavirus disease 2019 patients

Study [ref.]	Location	Subjects n	Age#	Female	Type of patient	Smoking rate	COPD rate	COPD prevalence by outcome		p-value
Guan [8]	China	1099	47.0	41.9%	Hospitalised and outpatients	Current 12.6%; former 1.9%	1.1%	Severe Non-severe Met primary endpoint¶ Did not meet primary endpoint	3.5% 0.6% 10.4% 0.5%	NA NA
Wang [10]	China	138	56	45.7%	Hospitalised	NA	2.9%	ICU Non-ICU	8.3% 1.0%	0.054
Zhou [11]	China	191	56.0	38%	Hospitalised	Current 6%	3%	Survivor Non-survivor	7% 1%	0.047
Huang [12]	China	41	49.0	27%	Hospitalised	Current 7%	2%	ICU Non-ICU	8% 0	0.14
Guan [13]	China	1590	48.9	42.7%	Hospitalised	Current and former 7%	1.5%	Severe Non-severe ICU Non-ICU Mechanical ventilation No mechanical ventilation Survivor Non-survivor	62.5% 15.3% 29% 5.9% 20.8% 2.9% 25% 2.8%	NA
Zhang [14]	China	140	57	49.3%	Hospitalised	Current 1.4%; former 5.0%	1.4%	Severe Non-severe	3.4% 0	0.170
Liu [15]	China	78	38	50.0%	Hospitalised	Current and former 6.4%	10%	Progression Improvement	9.1% 1.5%	0.264
Feng [16]	China	476	53	43.1%	Hospitalised	9.7%+	4.6%	Critical Severe Moderate	15.7% 5.6% 2.3%	<0.001
Li [17]	China	548	60	49.1%	Hospitalised	Current 7.5%; former 9.4%	3.1%	Severe Non-severe	4.8% 1.4%	0.026
Wang [18]	China	85	59.4	47.1%	Hospitalised	NA	5.9%	Severe Non-severe	10.3% 2.2%	0.265
Yan [19]	China	1004	62§; 68f	50.9%	Hospitalised	46.0%+	0.8%	Survivors Non-survivors	0.8% 0	0.563
Xiong [20]	China	421	52	49.2%	Hospitalised	NA	4.3%	Severe Recovered	1.7% 4.7%	0.478
Lv [21]	China	354	62	50.56%	Hospitalised	NA	1.69%	Critical Severe Mild	1.19% 1.94% 1.74%	NA
Zheng [90]	China	34	66	32.4%	ICU	NA	5.9%	Intubated Non-intubated	6.7% 5.3%	1.00
Cai [22]	China	383	61##; 44.5¶¶	36.3%##; 57.2%¶¶	Hospitalised	NA	8.4%	Severe Non-severe	14.3% 6.51%	0.03
Chen [23]	China	548	56.0	42.9%	Hospitalised	Ever 5.8%	1.3%	Survivors Non-survivors	0.4% 4.9%	NA
Shi [24]	China	671	63	52%	Hospitalised	NA	3.4%	Survivors Non-survivors	3.4% 3.2%	1.00
Zou [25]	China	154	60.68	56.49%	Hospitalised	8.44%+	5.84%	Survivors Non-survivors	2.94% 11.54%	0.074
Hu [26]	China	323	61	48.6%	Hospitalised	11.8%+	1.9%	Critical Severe Non-severe	3.8% 3.4% 0	0.033

Continued

TABLE 1 Continued

Study [ref.]	Location	Subjects n	Age#	Female	Type of patient	Smoking rate	COPD rate	COPD prevalence by outcome		p-value
Zhang [27]	China	111	38.0	65%	Hospitalised	NA	2.7%	Deterioration Discharge	5.6% 2.2%	0.415
Chu [91]	China	33	65.2	33.3%	ICU	NA	3.0%	ECMO No ECMO	14.3% 0	0.21
Wang [28]	China	107	51.0	46.7%	Hospitalised	NA	2.8%	Survivors Non-survivors	2.3% 5.3%	0.447
Lagi [46]	Italy	84	62	34.5%	Hospitalised	Current 7.1%; former 22.6%	5.6%	ICU Non-ICU hospitalisation	18.8% 2.9%	0.045
Tomlins [92]	UK	95	75	37%	Hospitalised	NA	11%	Survivors Non-survivors	8% 20%	0.2
Israelsen [93]	Denmark	175	71	51.4%	Hospitalised	Ever 55.8% Never 44.2%	6.3%	ICU Non-ICU hospitalisation	7.4% 6.1%	1.00
Auld [94]	Atlanta, GA, USA	217	64	45.2%	ICU	NA	9.7%	Survivors Non-survivors	9.5% 8.1%	0.737
Buckner [95]	Seattle, WA, USA	105	69	50%	Hospitalised	Ever 26%	10%	Severe Non-severe	14% 7%	NA
Javanian [96]	Iran	100	60.12	49%	Hospitalised	NA	12%	Survivors Non-survivors	8.64% 26.31%	0.032
Itelman [97]	Israel	162	52	35.2	Hospitalised	8.9%+	1.2%	Severe Moderate Mild	3.8% 0 1.1%	0.364
Lian [29]	China	788	68	57.4%	Hospitalised	Current 5.88%	2.2%	NA		
Liu [30]	China	137	57	55.5%	Hospitalised	NA	1.5%	NA		
Wu [31]	China	80	44	48%	Hospitalised	NA	4%	NA		
Xu [32]	China	90	50	57%	Hospitalised	NA	1%	NA		
Zhu [33]	China	32	46	53%	Emergency room	19%+	6%	NA		
Huang [34]	China	34	56.2	58.8%	Hospitalised	NA	8.8%	NA		
Wang [9]	China	63	39.3	46%	Asymptomatic	NA	1.6%	NA		
Zhang [35]	China	326	51	47.54%	Hospitalised	NA	0.61%	NA		
Liu [36]	China	238	55.0	42.0%	Hospitalised	NA	1.3%	NA		
Lian [37]	China	465	45	47.7%	Hospitalised	NA	0	NA		
Hong [38]	China	75	46.37	45%	Hospitalised	NA	0	NA		
Ji [39]	China	101	51.0	52%	Hospitalised	5%+	2%	NA		
Qiu [40]	China	104	43	52.88%	Hospitalised	3.85%+	0.96%	NA		
Wei [41]	China	101	49	46.5%	Hospitalised	7.9%+	1.0%	NA		
Grasselli [49]	Italy	1591	63	19%	ICU	NA	4%	NA		
Cecconi [47]	Italy	239	63.9	29.3%	Hospitalised	NA	9.2%	NA		
Inciardi [48]	Italy	99	67	19%	Hospitalised	20%+	9%	NA		
de Abajo [98]	Spain	1139	69.1	39.0%	Hospitalised	NA	10.5%	NA		
Barrasa [51]	Spain	48	63.2	43%	ICU	19%+	38%	NA		
Szekely [99]	Israel	100	66.1	37%	Hospitalised	8%+	4%	NA		
Richardson [42]	NYC	5700	63	39.7%	Hospitalised	15.6%+	5.4%	NA		
Goyal [43]	NYC	393	62.2	39.4%	Hospitalised	NA	5.1%	NA		
Kuno [44]	NYC	8438	59	46.1%	Hospitalised and outpatients	NA	2.4%	NA		
Palaiodimos [45]	NYC	200	64	51%	Hospitalised	Current and former 32.5%	14.0%	NA		
Arentz [52]	Washington state, USA	21	70	48%	ICU	NA	33.3%	NA		
Bhatraju [50]	Seattle, WA, USA	24	64	38%	ICU	NA	4%	NA		

Continued

TABLE 1 Continued

Study [ref.]	Location	Subjects n	Age #	Female	Type of patient	Smoking rate	COPD rate	COPD prevalence by outcome	p-value
Price-Haywood [100]	Louisiana, USA	3481	55.5++; 53.6§§	60%	Hospitalised and outpatients	NA	2.3%	NA	
Ferguson [101]	California, USA	72	60.4	47.2%	Hospitalised	Ever 27.4%	4.2%	NA	
Gold [102]	Georgia, USA	305	60	50.5%	Hospitalised	Current 5.2%	5.2%	NA	
Rentsch (preprint) [103]	USA	585	66.1	4.6%	Hospitalised and outpatients	Current 27.2%; former 30.6%; never 36.9%	15.4%	NA	
Mitra [104]	Canada	117	69	32.5%	ICU	Current and former 13.7%	6.8%	NA	

NYC: New York City, NY, USA. #: median or mean ages, years; ¶: ICU, mechanical ventilation or death; +: smoking status (*i.e.* current or former) not specified; §: age for survivors; f: age for non-survivors; ##: severe cases; ¶¶: non-severe cases; ++: age for white patients; §§: age for black patients. NA: not available.

21 patients, where 33% had COPD [52], although the small size of these studies must be kept in mind. To provide context, the prevalence of COPD in northern Italy, Spain, New York state, and Washington state is 11.7% [53], 10.2% [54], 5.8% [55], and 4.1% [56], respectively. Other cohorts that have reported more broadly on chronic pulmonary diseases without necessarily specifying COPD still show considerable variability. These numbers have ranged from as low as 2.0% in a Shanghai cohort of 249 hospitalised patients, to up to 17.7% of 20 133 hospitalised patients in the UK. Still, these numbers are less than those reported for other comorbidities, such as hypertension and diabetes.

Nonetheless, there is increasing evidence that COPD may be a risk factor for more severe COVID-19 disease [57]. An analysis of comorbidities in 1590 COVID-19 patients across China found that COPD carried an odds ratio of 2.681 (95% CI 1.424–5.048; p=0.002) for ICU admission, mechanical ventilation or death, even after adjustment for age and smoking [13]; 62.5% of severe cases had a history of COPD (compared with only 15.3% in non-severe cases) and 25% of those who died were COPD patients (compared with only 2.8% in those who survived). In a multicentre Chinese study, COPD patients made up 15.7% of the critically ill patients, but only 2.3% of moderately ill patients (p<0.001) [16]. Other studies have found similar, if statistically weaker, differences in COPD rates between ICU admissions and non-ICU admissions (8.3% *versus* 1.0%; p=0.054) [10], severe and non-severe cases (4.8% *versus* 1.4%; p=0.026) [17], and between non-survivors and survivors (7% *versus* 1%; p=0.047) [11].

The COPD airway in COVID-19

Why COPD patients appear to suffer worse outcomes upon contracting COVID-19 (even if their risk of contracting to begin with may not be high) is worth some speculation. First, recent evidence that COPD patients and smokers may display the machinery required for SARS-CoV-2 cellular entry differently has come to light. Similar to SARS-CoV (which was responsible for the 2002–2003 SARS pandemic) [58], SARS-CoV-2 bears an envelope spike protein that is primed by the cellular serine protease TMPRSS2 to facilitate fusion of the virus with the cell's angiotensin-converting enzyme 2 (ACE-2) receptor and subsequent cell entry (figure 1) [59–62]. Our group has recently demonstrated that in three separate cohorts with available gene expression profiles from bronchial epithelial cells, ACE-2 expression was significantly elevated in COPD patients compared to control subjects [63]. Current smoking was also associated with higher ACE-2 expression compared with former and never smokers, an observation which has subsequently been validated by other groups in separate cohorts of lung tissue and airway epithelial samples [64–66] and supported by additional evidence linking ACE-2 expression with nicotine exposure [67, 68]. It is important to note, though, that ACE-2 expression alone has not been shown yet to confer increased susceptibility or increased severity of disease. Moreover, the relatively low expression of ACE-2 in the bronchial epithelium in comparison to the nasal epithelium [69] has unclear implications for disease susceptibility in patients with predominantly small airways pathology.

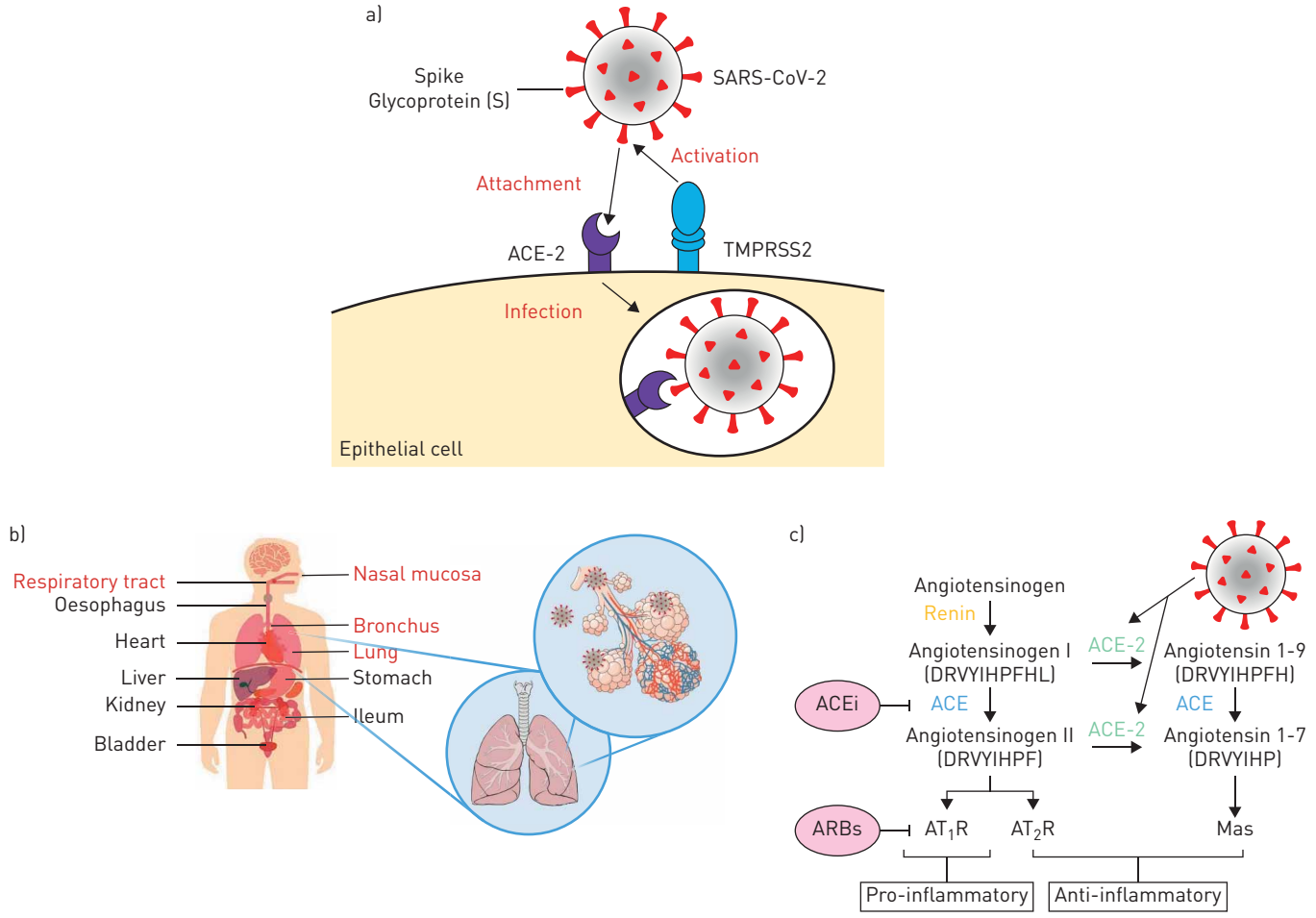

FIGURE 1 Schematic representation of a) severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binding to the angiotensin-converting enzyme 2 (ACE-2) receptor following activation of the spike protein (s) by transmembrane serine protease 2 (TMPRSS2), which leads to endocytosis and infection. b) Human organs that have been reported by Zou *et al.* [105] to show ACE2 expression, with the respiratory system highlighted in red. c) The renin–angiotensin system (RAS) and the proposed SARS-CoV-2 action. The generation of angiotensin II from angiotensin I by angiotensin-converting enzyme (ACE) induces vasoconstriction of blood vessels and pro-inflammatory effects through the binding of angiotensin II receptor type 1 (AT_1R), while the receptor type 2 (AT_2R) may negatively regulate this pathway. ACE inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) are very successful anti-hypertensives by promoting vasodilation of blood vessels. ACE-2 inhibits the activity of angiotensin II by converting angiotensin I to angiotensin 1–9 and angiotensin II to angiotensin 1–7, which binds to the MAS1 proto-oncogene (Mas) receptor with anti-inflammatory effects. Upon SARS-CoV-2 binding to ACE-2, there is a shift in the ACE/ACE-2 balance towards a predominance of ACE, resulting in increased pro-inflammatory effects and tissue damage.

The management of COPD patients during the COVID-19 pandemic

Two challenges of clinical care in COPD have emerged during this pandemic: 1) whether the usual algorithms of pharmaceutical management in COPD still apply and 2) how to weather the dramatic curtailments in non-pharmaceutical interventions this pandemic has wrought. Although our understanding of COVID-19 has substantially increased in a short period of time, these problems have largely been the domain of expert opinion rather than being guided by rigorous scientific evidence.

Questions remain about the effects of common respiratory medications used by our COPD patients such as inhaled (ICS) and systemic corticosteroids, short- and long-acting β_2-agonists, and short- and long-acting muscarinic antagonists in either mitigating or exacerbating COVID-19 infections. The epidemiological data emerging from China and other early epicentres have not yet provided the necessary granularity required to determine whether these medications are harmful or beneficial in COVID-19 patients with COPD. Peters *et al.* [70], however, have recently shown that ACE-2 expression in airway epithelial cells obtained from asthmatic patients was decreased in those taking ICS compared to those who were not on ICS, raising the possibility that ICS exposure could decrease viral entry. Whether the same relationship holds true in the COPD airway, in which the predisposition to pneumonia following ICS use is well-documented, has not yet been established. For now, in the absence of data demonstrating definitive

harm or benefit, ICS and other long-acting inhalers should not be routinely withdrawn nor should their use be escalated as a preventative measure for COPD patients during this pandemic [71].

Of greater concern is the use of systemic corticosteroids, the backbone of COPD exacerbation treatment. On balance, the historical evidence for systemic corticosteroids in viral pandemics has not been entirely favourable. Lessons from the SARS and Middle East respiratory syndrome (MERS) pandemics suggest potential harm, in fact. In SARS, while the majority of studies were inconclusive, four studies showed harm, including delayed viral clearance and increased rates of psychosis [72]. In MERS, corticosteroid use was associated with increased mortality [73] and delayed viral clearance [74]. So far, the most promising preliminary data on corticosteroids and COVID-19 are from a randomised controlled trial of dexamethasone (RECOVERY) performed in the UK, which demonstrated a one-third reduction in mortality [75]. Published data, however, are derived from small retrospective studies and appear mixed, with two studies showing no benefit [76, 77] and two studies showing improvements in rates of death and escalation of care [78, 79]. Because of the results of the RECOVERY trial, however, it is likely that dexamethasone will become standard of care treatment for COVID-19 patients including those with COPD.

The impact of the pandemic has been keenly felt by COPD patients in myriad aspects of their lives. Face-to-face clinic visits with their physicians have been curtailed, as have pulmonary rehabilitation sessions and COPD home visit programmes. Patients who may have normally presented to the hospital during an exacerbation might choose to stay home for fear of exposure, resulting in delayed care, as has occurred in other conditions like myocardial infarction [80, 81]. The long-term effects of this pause in routine care have yet to be measured. For now, healthcare systems have had to adapt to these conditions by augmenting telehealth and virtual visits. Fortunately, multiple randomised controlled trials assessing telehealth for COPD patients have demonstrated its feasibility and at least non-inferiority to usual care when it comes to exacerbations, hospitalisations and quality of life [82–86]. Moreover, online pulmonary rehabilitation programmes appear to be as effective as in-person sessions [87–89]. In the event that social distancing measures remain in place for many more months, we advocate for the establishment of these virtual programmes to ensure our patient population can continue to receive optimal care.

Directions for COVID-19 and COPD research

Specifically, we will have to address the following questions on COVID-19 as they pertain to COPD:

- Does the burden of disease, clinical manifestations, and outcomes of COVID-19 in COPD patients differ from the general population and if so, how?
- Given the multiple phenotypes associated with the term "COPD" (*i.e.* frequent exacerbators, emphysema-predominant, eosinophilic-predominant, asthma overlap), does COVID-19 infection in each of these phenotypes present and behave differently?
- Are routine medications used in COPD such as inhaled and systemic corticosteroids, β_2-agonists, muscarinic antagonists and chronic azithromycin protective or harmful in the setting of COVID-19 infection?
- What will the impact of post-COVID-19 infection disability be in COPD patients and what resources will be required to adequately support the transition of COPD patients from the hospital to home after COVID-19?
- How can we manipulate the unique airway pathology of COPD patients and the ACE-2 system to identify novel therapeutics?
- What is the role of inhaled substances (*e.g.* tobacco, cannabis and e-cigarettes) and air pollution in increasing the susceptibility of COPD patients to COVID-19?
- What can we learn from the experience of virtual care to COPD patients during this pandemic that can be applied in future scenarios to reach isolated patient populations and resource limited settings?

These research questions can best be answered by developing standards for transparent data reporting across the globe and harnessing the power of international networks that can quickly collate the data of COVID-19 COPD patients. Similarly, the efforts of translational research scientists at the laboratory bench who are working to characterise the pathophysiology of COVID-19 infections in the airway are critical to developing new therapies for a world in which there are currently very few.

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