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Prediction of in-hospital mortality of patients with SARS-CoV-2 infection by comorbidity indexes: an Italian internal medicine single center study

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Abstract. – OBJECTIVE: Clinical outcomes in patients hospitalized for severe acute respiratory syndrome due to coronavirus (SARS-CoV-2) infection seems to be closely related with burden of comorbidities. A comorbidity score could help in clinical stratification of patients admitted to internal medicine units. Our aim was to assess a novel modified Elixhauser index (mEi) and the Charlson Comorbidity Index (CCI) for predicting in-hospital mortality (IHM) in internal medicine patients with SARS-CoV-2 infection.

PATIENTS AND METHODS: This single-center retrospective study enrolled all consecutive patients discharged from internal medicine unit with confirmed SARS-CoV-2 infection. Both the mEi and CCI were easily calculated from administrative data. Comorbidity scores were tested using receiver operating characteristic (ROC) analysis, and the respective area under the curve (AUC).

RESULTS: The total sample consisted of 151 individuals, and 30 (19.9%) died during their hospital stay. Deceased subjects were older (82.8±10.8 vs. 63.3±18.1 years; $p<0.001$) and had a higher burden of comorbidities: the mEi and CCI were 29.9±11 vs. 8.8±9.2 and 4.6±2.6 vs. 1.2±2 ($p<0.001$), respectively. Only the mEi was independently associated with IHM (OR 1.173), and ROC curves analysis showed that the AUCs were 0.863 and 0.918 for the CCI and for mEi, respectively.

CONCLUSIONS: In patients admitted to internal medicine wards with SARS-CoV-2 infection, the mEi showed a better performance in predicting IHM than CCI.

Key Words:
In-hospital mortality, Internal medicine wards, Comorbidity, Comorbidity score, Charlson Comorbidity Index, Elixhauser index, SARS-CoV-2 infection.

Introduction

On December 31, 2019, a cluster of patients with pneumonia of unknown cause was linked epidemiologically to the Huanan Seafood Wholesale Market in Wuhan, Hubei Province, China. A previously unknown beta-coronavirus, isolated from airway epithelial cells from patients with pneumonia, was named 2019-nCoV[1]. Three weeks later (January 20, 2020), the first confirmed case of 2019-nCoV infection in the United States, was reported in Snohomish County, Washington[2]. During the first 2 months of the outbreak, COVID-19 spread rapidly throughout China. Of the 7736 patients with coronavirus disease (COVID-19) hospitalized at 552 sites at the end of January, Chinese colleagues obtained data

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regarding symptoms and outcomes for 14.2% of patients (n=1099, 41.9% women). The median age was 47 years, and the most common symptoms were fever (43.8%) and cough (67.8%). Diarrhea was uncommon (3.8%). The median incubation period was 4 days (interquartile range, 2 to 7). On admission, ground-glass opacity was the most common radiologic finding on chest computed tomography (CT) (56.4%), and lymphocytopenia was present in 83.2% of the patients on admission[3]. In Italy, the current mortality rate due to Severe Acute Respiratory Syndrome due to coronavirus (SARS-CoV-2) infection is high, at least in part due to the high proportion of subjects aged ≥65 years with multiple comorbidities[4]. In April 20, 2020, a total of 21,551 deaths related to COVID-19 were reported in Italy. The median age of deceased subjects was 79 years, 15 years higher than that of the national sample diagnosed with the virus (64 years). The great majority of deaths occurred in men aged ≥70 years. The most common comorbidities diagnosed in deceased subjects were: hypertension (69.7%), type 2 diabetes (31.9%), ischemic heart disease (27.4%), atrial fibrillation (21.7%), chronic renal failure (21.4%), chronic obstructive pulmonary disease (17.3%), active cancer in the past 5 years (15.9%), heart failure (15.8%), dementia (14.8%), obesity (12.2%), and stroke (10.9%). Regarding the total number of coexisting comorbidities, three or more, two, one, and no comorbidity were documented in 60.7, 21.2, 14.4, and 3.7% of deceased subjects, respectively[5].

The relationship between comorbidity and death was also reported in a Chinese study. The authors described 41 patients admitted with SARS-CoV-2 infection (73% men): 20% had diabetes, 15% hypertension, 15% cardiovascular disease, 32% were admitted to intensive care units, and 15% had a fatal outcome[6]. Another Chinese study investigated 99 patients, and 51% had chronic conditions: cardiovascular and cerebrovascular diseases in 40% of patients, endocrine diseases in 13%, digestive diseases in 11%, and malignant tumor, nervous system diseases, and respiratory diseases (1% each). Deceased subjects comprised 11% of cases[7]. Other Chinese studies suggested that, in addition to age and hypertension, biochemical parameters, such as oxygenation index, double lung patch, decreased lymphocyte count, and elevated levels of C-reactive protein, aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and creatine kinase (CK) were predictors of disease severity[8]. The relationship between SARS-CoV-2 infection and associated chronic conditions is still a matter of debate.

To evaluate the impact of comorbidity on outcome, it is necessary to measure its burden. To calculate a precise estimation, two methods are available: (i) a simple count of diseases in each individual, and (ii) validated scores able to assess the morbidity burden by means of different weights assigned to specific diseases, based on their severity and association with the risk of mortality[9]. In 2017, we proposed a modification of the Elixhauser Index[10], adapting it to internal medicine patients, and obtained a new index of comorbidity to predict risk for in-hospital mortality (modified Elixhauser index, mEi)[11]. This novel score was further utilized in the case of hospital admissions in internal medicine units due to infections, and it was shown to predict IHM, with Receiver Operating Characteristic (ROC) analysis showing an area under the curve (AUC) of 0.724[12]. Since the outbreak of Coronavirus infection was followed by an abrupt increase in hospital admissions, much higher than the intensive care and pulmonology units' availability, a large percentages of Italian internal medicine units were quickly adapted to receive COVID patients. Thus, we decided to test the mEi on COVID-19 patients admitted to internal medicine units. The aim of the present study was to evaluate this novel score and the Charlson Comorbidity Index (CCI), comparing their performance in predicting IHM in a consecutive cohort of patients discharged from an internal medicine ward for infection due to SARS-CoV-2.

Patients and Methods

Population and Administrative Data Source

This retrospective study was conducted in agreement with the Declaration of Helsinki of 1975, revised in 2013. Subject identifiers were deleted before data analysis aiming at maintaining data anonymity and confidentiality; therefore, none of the patients could be identified, either in this paper or in the database. The study was conducted in agreement with the existent Italian disposition-by-law (G.U. No. 76, 31/03/2008), and due to the study design, the Ethics Committee approval was not mandatory.

Ferrara is a province located in the Eastern part of the Emilia-Romagna region of Italy, with a

total population of approximately 350,000 inhabitants, characterized by a high presence of elderly subjects (~26% of total population is aged >65 years, and nearly 1% >90 years). The General and University Hospital (Azienda Ospedaliero-Universitaria "S. Anna"), is provided with 626 beds and represents the hub and teaching hospital of the entire province. The annual flow of patients by the emergency department (ED) is approximately 90,000. The "S. Anna" Hospital approached the Coronavirus outbreak with a series of organizational measures. A specific COVID-dedicated pathway was adopted, including the ED triage area, the Infectious Disease and a "suspect" observational unit, three Internal Medicine units, one Pulmonology unit, and one Intensive Care Unit. This study included all patients discharged from the COVID internal medicine units for SARS-CoV-2 infection along the first month of this dedicated pathway, from March 15 to April 15, 2020. Data from the Discharge Hospital Records (DHR) included sex, date of birth, date and department of hospital admission and discharge, vital status at discharge, length of stay, main and up to 6 accessory discharge diagnoses, and the most important diagnostic procedures, based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Data have been completely blinded, and each possible and/or potential identifier was removed from the database provided for this study, in agreement with national dispositions by law in terms of privacy.

The internal medicine COVID units, 24/24 h and 7/7 days open to the ED admissions, accounted for a total of 88 beds, and received only confirmed SARS-CoV-2 infection (positive polymerase chain reaction, tested by nasopharyngeal swab).

Comorbidity Score Calculation

(i) Charlson Comorbidity Index (CCI). The CCI appeared in the international literature four decades ago, and was based on the mortality rates of patients admitted to the general internal medicine service. It predicts survival in patients with multiple comorbidities, and is widely used as a measure of total comorbidity burden[13]. When the score is 0, the corresponding estimated 10-year survival rate is 98%, and such estimation decreases with increasing age in decades older than 50 years of age, and with comorbidities. Overall, sixteen diseases are included, i.e., myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic obstructive pulmonary disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, moderate to severe chronic kidney disease, solid tumor, leukemia, lymphoma, and AIDS. Each condition has different weights, and if the final total score is ≥7, the corresponding 10-year survival rate is estimated to be 0%[13].

(ii) Modified Elixhauser index (mEi). This novel score represents a specific development of a modified Elixhauser Index, recently proposed by our group for patients admitted to internal medicine units[11] and based on Quan et al[14] guidelines. The score includes the following conditions: age, sex, presence of renal diseases, neurological disorders, lymphoma, solid tumor with metastasis, ischemic heart disease, congestive heart disease, coagulopathy, fluid and electrolyte disorders, liver disease, weight loss, and metastatic cancer. Each condition is related to different points and the sum of the different points represents the score. The points assigned to each condition ranged from 0 to 16, and the possible range of the score varied between 0 and 89. IHM risk is significant when the score is >40, overcoming the value of 60%[11].

Statistical Analysis

We chose IHM as the primary hard outcome. A descriptive analysis was carried out, and results are expressed as absolute numbers, percentages, and mean ± SD. Univariate analysis defined the difference between survivors and deceased subjects, and Chi-square test, Student *t*-test, and Mann-Whitney test were used as appropriate. Moreover, a logistic multivariate analysis was performed aiming at defining the variables independently associated with IHM. Finally, we estimated ROC curves, to weight prediction power on IHM; the AUCs and 95% confidence intervals (95% CIs) were calculated. SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

Results

During the one-month study period, 151 individuals were discharged from our internal medical wards dedicated to COVID-19. The mean age was 66.4±18.7 years, 72 (47.7%) were males, and the mean length of stay was 13.3±8.9 days. Hypertension was recorded in 51.7% of cases and diabetes in 17.2%, and the mean values of mEi

Table I. Main characteristics of the 151 investigated individuals.

Age (years)	66.4 ± 18.7
Female [n (%)]	79 (52.3%)
Male [n (%)]	72 (47.7%)
Hypertension [n (%)]	78 (51.7%)
Diabetes mellitus [n (%)]	26 (17.2%)
Congestive Heart Failure [n (%)]	9 (6%)
Solid Tumor without Metastasis [n (%)]	34 (22.5%)
Metastatic Cancer [n (%)]	6 (4%)
Renal Failure [n (%)]	24 (15.9%)
Neurological Disorders [n (%)]	43 (28.5%)
Myocardial infarction [n (%)]	12 (7.9%)
Coagulopathy [n (%)]	18 (11.9%)
Weight Loss [n (%)]	22 (14.6%)
Fluid and Electrolyte Disorders [n (%)]	14 (9.3%)
Liver Disease [n (%)]	5 (3.3%)
Charlson Comorbidity Index	1.9 ± 2.5
Modified Elixhauser index	13 ± 12
Length of stay (days)	13.3 ± 8.9
In-hospital mortality [n (%)]	30 (19.9%)

and CCI were 13±12.7 and 1.9±2.5, respectively. IHM was recorded in 30 patients (19.9%). The main characteristics of the population are reported in Table I.

Age, CCI and mEi were higher in deceased individuals than in survivors; moreover, the prevalence rates of congestive heart failure, renal failure, neurological disorders, myocardial infarction, weight loss, and fluid and electrolyte disorders were higher in deceased individuals (Table II).

Only the mEi was independently associated with IHM, (OR 1.173, 95%C.I. 1.096-1.256, $p<0.001$), while CCI was not. ROC analysis showed that mEi (AUC 0.918; 95%CI 0.870-0.966, $p<0.001$) and CCI (AUC 0.863; 95%CI 0.794-0.932, $p<0.001$) were significant predictors of IHM (Figure 1).

Discussion

In this study, we aimed to test mEi and CCI in patients admitted to internal medicine wards with SARS-CoV-2 infection. To the best of our knowledge, this is the first study designed for comparison of the predictive role for IHM of two comorbidity scores. Both indexes could be considered predictors of worse outcome, although mEi seems to show better results than CCI with focused reference on IHM. Contrary to previous findings, single frequent comorbidities, such as hypertension and diabetes were not independently associated with IHM, at least when analyzing this limited cohort of patients. As expected, the mean age of deceased individuals was 20 years higher than survivors, and we did not find any difference by sex. In the last decade, we have investigated several large cohorts suffering from a series of medical diseases, always finding a significant relationship between comorbidity and IHM[15-24]. Moreover, we have positively tested the mEi in patients with infectious diseases admitted to internal medicine units to evaluate IHM[12].

As SARS-CoV-2 infection has emerged as a global health problem only since February 2020, characteristics and risk factors associated with disease severity and mortality, as well as associ-

Table II. Comparison between deceased and survivors.

	Survivors (n = 121)	Deceased (n = 30)	p
Age (years)	62.3 ± 18.1	82.8 ± 10.8	< 0.001
Male/Female [n (%)]	61 (50.4)/60 (49.6)	11 (36.7)/19 (63.3)	NS
Hypertension [n (%)]	60 (49.6%)	18 (60%)	NS
Diabetes mellitus [n (%)]	18 (14.9%)	8 (26.7%)	NS
Congestive Heart Failure [n (%)]	2 (1.7%)	7 (23.3%)	< 0.001
Solid Tumor without Metastasis [n (%)]	25 (20.7%)	9 (30%)	NS
Metastatic Cancer [n (%)]	3 (2.5%)	3 (10%)	NS
Renal Failure [n (%)]	12 (9.9%)	12 (40%)	< 0.001
Neurological Disorders [n (%)]	22 (18.2%)	21 (70%)	< 0.001
Myocardial infarction [n (%)]	5 (4.1%)	7 (23.3%)	0.001
Coagulopathy [n (%)]	13 (10.7%)	5 (16.7%)	NS
Weight Loss [n (%)]	5 (4.1%)	17 (56.7%)	< 0.001
Fluid and Electrolyte Disorders [n (%)]	2 (1.7%)	12 (40%)	< 0.001
Liver Disease [n (%)]	3 (2.5%)	2 (6.7%)	NS
Charlson Comorbidity Index	1.2 ± 2.0	4.6 ± 2.6	< 0.001
Modified Elixhauser index	8.8 ± 9.2	29.9 ± 11	< 0.0101
Length of stay (days)	13.8 ± 9.3	11.1 ± 6.8	NS

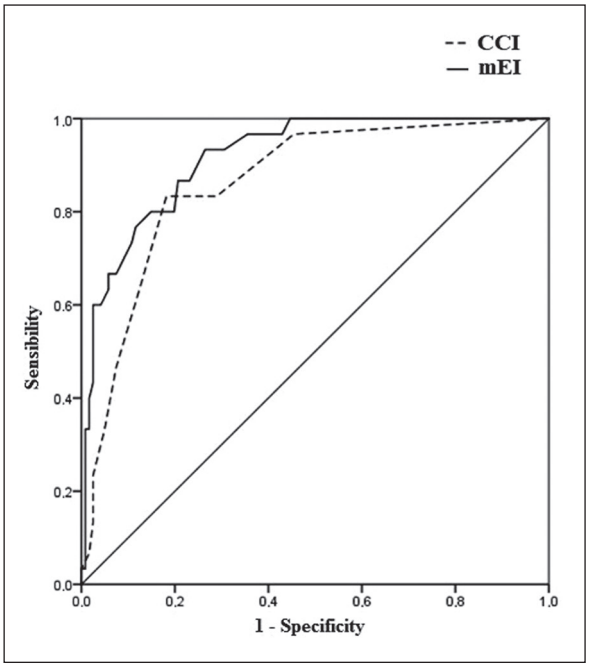

Figure 1. Receiver operating characteristics (ROC) curves for predicting in-hospital mortality (IHM). The area under curve (AUC) and 95% confidence intervals (95% CIs) were 0.918 (95% CI 0.870-0.966, $p<0.001$), and 0.863 (95% CI 0.794-0.932, $p<0.001$) for modified Elixhauser index (mEi) and Charlson Comorbidity Index (CCI), respectively.

ated comorbidities, can only be extrapolated by the data published in this short time window, and mainly from Chinese studies.

Age and Sex

In the study by Zhang et al[25], subjects older than 60 years and those with chronic diseases suffering from severe and critical COVID-19 conditions, showed no improvement and high mortality, and factors associated with worse conditions were male sex, expectoration, muscle ache, and decreased albumin[25]. In another study, male sex and older age, together with leukocytes, high LDH level, cardiac injury, hyperglycemia, and high-dose corticosteroid use, were reported to be associated with fatal outcome in the cohort of severe COVID patients by Li et al[26]. In their retrospective study on 191 patients (28% of whom with fatal in-hospital outcome), Zhou et al[27] reported a 48% presence of comorbidities, with hypertension, diabetes mellitus, and coronary heart disease present in 30%, 19% and 8% of cases, respectively. IHM was associated with older age, higher Sequential Organ Failure Assessment (SOFA) score, and d-dimer levels >1 μg/mL on admission[27]. Age was also a crucial point in the study by Guan et al[3]. After categorizing COVID-19 patients on admission as nonsevere or severe (84% and 16%, respectively), patients with severe disease were older by a median of 7 years and showed a higher presence of coexisting illness (38.7% *vs.* 21.0%)[3]. A prognostic nomogram, obtained on approximately 1600 hospitalized subjects throughout China to predict the survival of patient with COVID-19, indicated age (≥75 and 65-74 years), coronary heart disease, cerebrovascular disease, dyspnea, procalcitonin levels >0.5 ng/ml, and aspartate aminotransferase (AST) >40 U/liter, as factors independently associated with fatal outcome[28].

Other Comorbidities

Presence of kidney disease on admission and development of acute kidney injury during hospitalization have been associated with IHM in patients with COVID-19[29]. Diabetes is a risk factor for the progression and prognosis of COVID-19[30], and diabetic patients with COVID-19 have higher risk of mortality and internal care unit admission[31]. The results of a meta-analysis showed that hypertensive patients with COVID-19 infections had a significantly higher mortality risk compared with normotensive ones[32].

Prediction Models

Attention to prediction models has focused on critical patients. Wynants et al[33] critically evaluated prediction models for diagnosing COVID-19 in subjects with suspected infection, for prognosis and for detecting risk of admission for pneumonia, and concluded that proposed models showed high risk of bias and reported performance was optimistic[33]. The MuLBSTA (Multilobular infiltration, hypo-Lymphocytosis, Bacterial coinfection, Smoking history, hyper-Tension and Age) Score has been proposed to predict the risk of mortality in patients with viral pneumonia, but there has been no experience with 2019-nCoV infection so far[34]. In Italy, the Brescia-COVID-19 respiratory severity scale/algorithm has been proposed as a stepwise management approach to COVID-19 patients based on clinical severity[35].

The need to measure comorbidities and assess their validity and reliability is a matter of debate for several years, since the existing scores have pros and cons depending on the setting and object of study. For example, CCI, Cumulative Illness Rating Scale (CIRS), Index of Coexisting Disease (ICED), and Kaplan Index, which were specifi-

cally developed for use in diabetes research, were all considered valid and reliable methods to be used in clinical research. Some authors[36] have underlined that CCI was the most extensively studied score for predicting mortality. However, in 2012, a different systematic review stated that Elixhauser Index seemed to be the best predictor for short-term and long-term mortality[37]. A systematic review compared the capacity of morbidity measures to predict mortality among subjects admitted to internal medicine, geriatric, or all hospital wards, selecting inpatients aged ≥65 years. The results concluded that CCI was the most frequently used comorbidity score in internal medicine wards, and its predictive power was better during a longer follow-up period, but the Geriatric Index of Comorbidity was a better predictor of mortality risk[38].

The question is which score has greater potential to be utilized for evaluating in-hospital mortality in internal medicine units, where higher age and burden of comorbidities is the rule and not the exception. Moreover, different countries may show wide differences in age and comorbidities, also depending by their citizens' economic and social status. We are now making a wide use of data obtained from the recent Chinese experience, but it is important to stress that the median age of Chinese patients was 47 years[3]. New York City has recently emerged as the epicenter of COVID-19 in the United States, and data from the first 393 consecutive patients with COVID-19 hospitalized in New York City, reported a median age of 62.2 years, with a mortality of 10.2%[39]. In addition, Richardson et al[40] evaluated a large cohort of 5700 patients living in the New York City area (60% men), and the median age was 63 years. They calculated a median CCI of 4, indicating a significant comorbidity burden, corresponding to a 53% estimated 10-year survival. The highest percentage of death was recorded in male subjects aged ≥ 80 years, while the mortality was 0% for subjects aged < 20 years[40].

Limitations

Several limitations need to be declared. First, this is a single-center retrospective study, exclusively evaluating patients admitted to the internal medicine ward and conducted on a small population; therefore, the results could not be generalizable. Second, studies drawing clinical considerations based on ICD-9-CM codes, are characterized by a low sensitivity and specificity, since these indexes have been developed for financial reasons and not for research scope. Third, we evaluated only IHM; thus we did not have information on possible fatalities after a medium-term or long-term follow-up. Fourth, we did not take into consideration clinical parameters, but only the burden of comorbidity, based on ICD-9-CM codes. Thus, we lack data on clinical severity, functional status, or intensity of care given. Last, comorbidity indexes do not include all comorbidities that could be diagnosed in internal medicine patients, usually they include those with a precedent statistical process related to mortality.

Conclusions

Risk stratification has to be taken into account in everyday clinical practice, due to the aging of the population, and in cases of acute disease. In the setting of an internal medicine unit, this study seems to show that the mEi has a better performance in predicting IHM than CCI even for SARS-CoV-2 patients. Despite the limitations named above, we believe that the present study, based on clinical evident diagnosis, could be considered representative of everyday clinical practice. Although the number of subjects enrolled in this study is low, our findings could be interpreted as a first step, suggesting that in individuals with SARS-CoV-2 infection calculation of comorbidity burden could help patients' stratification. This also in consideration of a second phase of infection. In fact, after the first outbreak, characterized by patients admitted with high-severity disease features and needing intensive and respiratory care, the infection is now rapidly spreading to long-term care facilities. These facilities are high-risk settings for severe outcomes from outbreaks of COVID-19, with guests characterized by advanced age and multiple chronic comorbidities. Once COVID-19 is introduced into a long-term care facility, it has the potential to spread rapidly and widely. New data from a long-term care facility in the state of Washington, USA, showed hospitalization rates for residents, visitors, and staff of 54.5%, 50.0%, and 6.0%, respectively, and a residents' case fatality rate of 33.7%[41]. An appropriate estimation of the comorbidity burden and the underlying risk of IHM in subjects hospitalized for SARS-CoV-2 infection, could be a useful tool to plan more appropriate clinical assistance in internal medicine settings.

Disclosure Statement

There are no financial or other conflicts of interest incurred by any of the authors due to the sources of funding, or utilized products, technology, or methods of our research and report of findings.

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Authors' Contribution

Conceptualization, ADG, FF, and RM; methodology, ADG, and FF; software, ADG, FF, SG, and EDS; validation, RDG, AP, GZ, and RM; formal analysis, ADG, FF, SG, and EDS; investigation, ADG, SG, and EDS; resources, RDG, AP, GZ, and RM; data curation, ADG, SG, and EDS; writing-original draft preparation, A.D.G., and F.F.; writing-review and editing, R.D.G., AP, GZ, and RM; visualization, AGG, SG, EDS, and AP; supervision, AP, GZ, and RM; project administration, RDG, GZ, and RM; funding acquisition, FF. All authors have read and agreed to the published version of the manuscript.

Appendix List of Collaborators

OUTcome and **COM**orbidity **E**valuation of **INT**ernal **MED**icine **COVID19** (OUTCOME-INTMED-COV19) Study Collaborators.

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