ARTICLE

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Cancer increases risk of in-hospital death from COVID-19 in persons <65 years and those not in complete remission

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Abstract
The impact of cancer on outcome of persons with coronavirus disease 2019 (COVID-19) after infection with acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is controversial. We studied 1859 subjects with COVID-19 from seven centers in Wuhan, China, 65 of whom had cancer. We found having cancer was an independent risk factor for in-hospital death from COVID-19 in persons <65 years (hazard ratio [HR] = 2.45, 95% confidence interval [CI], 1.04, 5.76; $P = 0.041$) but not in those ≥65 years (HR = 1.12 [0.56, 2.24]; $P = 0.740$). It was also more common in those not in complete remission. Risks of in-hospital death were similar in subjects with solid cancers and those with hematological cancers. These data may help predict outcomes of persons with cancer and COVID-19.

Introduction

The impact of cancer on outcome of persons developing coronavirus disease 2019 (COVID-19) after infection with acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is controversial [1–12]. Several studies reported an increased risk of death [1–3, 5–9, 13–18], others not [19–26]. We studied 1859 subjects with COVID-19 from seven centers in Wuhan, China, 65 of whom also had cancer. We found cancer was an independent risk factor for in-hospital death from COVID-19 in subjects <65 but not ≥65 years. Subjects with cancer not in complete remission also had an increased risk of death from COVID-19. Risks of death were similar in subjects with solid cancers and those with hematological cancers. These data may help predict outcomes of persons with cancer and COVID-19.

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Methods

Study design and participants

Between 20 January and 4 April 2020 we studied 1859 consecutive subjects with COVID-19 treated at seven centers of five hospitals of Union Hospital (main part, Union West Hospital and Union Tumor Hospital), Wuhan Central Hospital, General Hospital of Central Theater Command, PLA and Wuhan Jinyintan Hospital. These hospitals were urgently reconstructed by the Chinese government as the designated hospitals and centers for COVID-19 therapy.

Subjects were tested for SARS-CoV-2-infection by qRT-PCR of nasal and pharyngeal swabs and/or blood test for anti-SARS-CoV-2 IgG/IgM antibodies using a colloidal-gold-based 2019-nCoV IgG/IgM Detection Kit (Nanjing Vazyme Medical Technology, Nanjing, China) using criteria of the Novel Coronavirus Pneumonia Diagnosis and Treatment Program of the National Health Commission of China (7th version) [27] and World Health Organization (WHO) interim guidance [28]. COVID-19 was diagnosed in neighborhood clinics or Fangcang Hospital before admission to the designated hospitals or in designated hospitals after admission [29]. Severity of COVID-19 was graded as described [2]. Subjects were treated as reported [30, 31] or according to Chinese government guidelines. The study was approved by the Ethics Committees of Union Hospital (2020-0095) and of Wuhan Central Hospital (2020-007). Requirement for informed consent was waived by the Ethics Committees.

Data collection

Electronic medical records (EMRs) of subjects including epidemiological, demographic, and laboratory data were reviewed. Outcomes included: (1) death; (2) alive with two successive negative SARS-Cov-2 qRT-PCR tests; (3) interval from symptoms to hospital admission, discharge or death; (4) negative qRT-PCT test; and (5) interval from admission to COVID-19 progression. Data collection forms were reviewed and verified independently by two physicians (WH and JY). A third researcher adjudicated discordances. Data were analyzed as of 24 April 2020.

Definitions

Solid cancers and hematological cancers were included. Cancer remission was defined as complete remission for ≥1 year. Exposure history was defined as contact with persons with confirmed SARS-CoV-2 infection or visit to the South China Seafood Wholesale Market. Smoking history was defined as current or former smoker (stopping >5 years ago) with exposure of ≥20 cigarettes per day for ≥1 year (1 pack

year). Fever was defined as temperature ≥37.3 °C. Acute kidney and heart injury and acute respiratory distress syndrome (ARDS) were defined as reported [32, 33]. Liver injury was defined as ≥1 liver function enzyme activity value ≥2 x upper limit of normal. Invasive and non-invasive mechanical ventilations were defined as mechanical ventilation with or without intubation [34, 35].

Statistical analysis

Continuous variables with a skewed distribution were described as median (interquartile range, IQR). Categorical variables are presented as number (%). Proportions for categorical variables were compared by $\chi 2$ test or Fisher exact test. Pearson $\chi 2$ test was used for contingency data for variables with more than two categories. Mann–Whitney test was used to compare continuous variables. Co-variates associated with risk of in-hospital death from COVID-19 were analyzed in a Cox regression model. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) calculated using the Cox proportional hazard model. Co-variates with $P < 0.05$ in uni-variable analyses except those with co-linearity were included in multi-variable analyses. Statistical analysis was performed with SPSS 26.0 statistical software (IBM Corporation, New York, United States). A two-sided P value < 0.05 was considered significant.

Results

Admission demographic and baseline co-variates

From 20 January to 4 April 2020, 3559 hospitalized persons who died or were discharged with COVID-19 were enrolled, 1859 of whom had quantitative real-time reverse transcriptase-polymerase chain reaction (qRT-PCR)- ($N = 1790$) or IgM/G ($N = 69$)-confirmed SARS-CoV-2-infection were included in the analysis. 1650 survived; 209 died. Age and age distribution, sex, smoking history, exposure history, co-morbidities, signs and symptoms at admission, radiological features by lung computed tomography (CT) scan and COVID-19 severity were displayed in Table 1.

Of the 1859 subjects, 65 (3%) had cancer 47 survived; 18 died. None of the 18 subjects died from cancer. Detailed data were available in 59 subjects (Supplement Table 1). Most had solid cancers including breast ($N = 8$), thyroid ($N = 7$) and gastric cancers ($N = 6$). 9 subjects had hematological cancers including lymphoma ($N = 4$), leukemia ($N = 3$), myelodysplastic syndrome ($N = 1$) and plasma cell myeloma ($N = 1$). Twenty-one subjects were diagnosed >5 years, 25, 1–5 years ago and 13, ≤1 year before their COVID-19 admission. In 41 subjects the cancer was in complete remission and in 18 in less than complete

Table 1 Demographic and clinical co-variates.

	Total $N = 1859$	Non-cancer $N = 1794$ (97)	Cancer $N = 65$ (3)	P-value
Co-variates				
Age, median (IQR), years	59 (45, 68)	59 (45, 68)	63 (54, 70)	0.054
Age				0.194
<65 years	1199 (65)	1162 (65)	37	
≥65 years	660 (36)	632 (35)	28	
Male	934 (50)	903 (50)	31	0.706
Smoking history	111 (6)	105 (6)	6	0.019
Former smoker	66 (4)	60 (3)	6	
Current smoker	45 (2)	45 (3)	0	
Exposure history				0.036
Huanan Seafood Market	4 (0.2)	3 (0.2)	1	
Close contact with infected persons	78 (4)	77 (4)	1	
Co-morbidity				
ASCVD	268 (14)	259 (14)	9	>0.999
Arterial hypertension	579 (31)	559 (31)	20	>0.999
Diabetes mellitus	262 (14)	250 (14)	12	0.303
COPD	61 (3)	60 (3)	1	0.722
Chronic kidney disease	45 (2)	44 (3)	1	>0.999
Gastro-intestinal disease	98 (5)	93 (5)	5	0.388
Signs and symptoms				
Fever[a]	1448 (78)	1399 (78)	49	0.608
Temperature (°C)[b]	36.6 (36.4, 37.0)	36.6 (36.4, 37.1)	36.6 (36.5, 36.9)	0.464
Shortness of breath	716 (39)	685 (38)	31	0.123
Dry cough	619 (43)	597 (43)	22	0.294
Wet cough	715 (39)	684 (38)	31	0.12
Fatigue	695 (37)	670 (37)	25	0.858
Nausea and/or vomiting	124 (9)	116 (8)	8	0.21
Diarrhea	243 (13)	234 (13)	9	0.852
Chills	281 (19)	274 (20)	7	0.137
Rhinorrhea	33 (2)	32 (2)	1	>0.999
Myalgia	315 (17)	305 (17)	10	0.867
Headache	107 (6)	105 (6)	2	0.583
Radiological co-variates				
Bilateral pneumonia	1570 (88)	1515 (88)	55	0.693
Consolidation	326 (19)	314 (18)	12	0.754
Ground-glass opacity	1331 (75)	1287 (75)	44	0.6
Patchy shadows	736 (42)	700 (41)	36	0.005
COVID-19 severity				0.003
Mild	34 (2)	33 (2)	1	
Moderate	1170 (63)	1141 (64)	29	
Severe	453 (24)	433 (24)	20	
Critical	202 (11)	187 (10)	15	

Data are median (IQR) or n (%).

ASCVD cardio- and cerebro-vascular disease, *COPD* chronic obstructive pulmonary disease

[a] ≥1 temperature ≥ 37.3 °C from onset of symptoms to admission.

[b] Admission temperature.

remission. No subjects were receiving anti-cancer therapy on admission for COVID-19. Sixteen of them received anti-cancer therapy <1 month before admission. Therapies included surgery ($N = 1$), chemotherapy ($N = 12$), targeted therapy ($N = 6$) and radiation therapy ($N = 1$). Demographic and clinical characteristics of COVID-19 subjects with cancers were shown in Supplement Table 2.

Comparison of cancer and non-cancer subjects with COVID-19 by admission clinical co-variates

Subjects with cancer were more likely to be old (median 63 years, interquartile range [IQR] 54–70 years versus 59 years, [IQR] 46–68 years; $P = 0.054$; Table 1), to be smokers (9% versus 6%, $P = 0.019$) and to have visited the Huanan Seafood Whole Sale Market (1 versus 3; $P = 0.036$). There were no significant differences in age distribution (57% versus 65%, <65 years; $P = 0.194$) or ≥1 prior co-morbidity (46% versus 47%; $P > 0.999$). Prior co-morbidities included ASCVD ($N = 9$), arterial hypertension ($N = 20$), diabetes mellitus ($N = 12$), COPD ($N = 1$), chronic kidney disease ($N = 1$) and gastro-intestinal disease ($N = 5$).

Signs and symptoms on admission including temperature, shortness of breath, dry and wet coughs, fatigue, nausea and/or vomiting, diarrhea, chills, rhinorrhea, myalgia and headache were similar between subjects with and without cancer. Subjects with cancer subjects were more likely to have patchy lung infiltrates on lung CT (60% versus 41%, $P = 0.005$) but similar frequencies of consolidation, bilateral pneumonia and ground-glass opacity. Subjects with cancer were more likely to have severe/critical COVID-19 severity on admission (54% versus 35%; $P = 0.003$).

Comparison of cancer and non-cancer subjects with COVID-19 by laboratory co-variates

Admission laboratory co-variates in subjects with and without cancer are displayed in Table 2. Cancer subjects had significant higher median concentrations of neutrophils (5×10 E + 9/L [IQR $3–7 \times 10$ E + 9/L] versus 3×10 E + 9/L [IQR $2–5 \times 10$ E + 9/L]; $P = 0.001$), neutrophil-to-lymphocyte ratio (NLR) (4 [IQR 3–8] versus 3 [IQR 2–5]; $P < 0.001$) and lower median concentrations of lymphocytes (0.9×10 E + 9/L [IQR $0.6–1.3 \times 10$ E + 9/L] versus 1.1×10 E + 9/L [IQR $0.8–1.6 \times 10$ E + 9/L]; $P < 0.001$) and hemoglobin ($120 \times$ g/L [IQR $102–132 \times$ g/L] versus $128 \times$ g/L [IQR $117–139 \times$ g/L]; $P < 0.001$). There were no significant differences in platelet concentrations or percentages of lymphocyte subsets including CD3-positive cells, CD4-positive cells, CD8-positive cells, natural-killer (NK) cells or B lymphocytes or in CD4-positive/CD8-positive ratio. Median plasma concentration of tumor necrosis factor (TNF)-α was lower in subjects with cancer (2.9 pg/ml [1.8–3.5 pg/ml] versus 3.4 pg/ml [2.2–5.5 pg/ml]; $P = 0.029$). Plasma concentrations of other cytokines including interleukin (IL)-4, IL-6, IL-10, and interferon (IFN)-γ were similar.

Cancer subjects had higher median serum concentrations of C-reactive protein (CRP, 27 mg/L [IQR 6–66 mg/L]

Table 2 Laboratory co-variates.

Co-variates (normal range)	N	Total	Non-cancer	Cancer	P value
CBC					
Neutrophils ×10 E + 9/L (1.8–6.3)	1816	3 (2, 5)	3 (2, 5)	5 (3, 7)	0.001
Lymphocytes ×10 E + 9/L (1.1–3.2)	1847	1.0 (0.8, 1.6)	1.1 (0.8, 1.6)	0.9 (0.6, 1.3)	0.001
Monocytes ×10 E + 9/L (0.1–0.6)	1805	0.4 (0.3, 0.5)	0.4 (0.3, 0.5)	0.4 (0.2, 0.7)	0.32
Hemoglobin, g/L (115–150)	1433	128 (117, 139)	128 (117, 139)	120 (102, 132)	<0.001
Platelets ×10 E + 9/L (125–350)	1814	203 (155, 264)	203 (155, 263)	216 (157, 284)	0.479
NLR	1814	3 (2, 5)	3 (2, 5)	4 (3, 8)	<0.001
Inflammation co-variates					
CRP, mg/L (<8)	1371	13 (3, 51)	13 (3, 49)	27 (6, 66)	0.047
Procalcitonin, ng/ml (<0.5)	1643	0.06 (0.05, 0.1)	0.05 (0.05, 0.1)	0.1 (0.06, 0.2)	0.001
LDH, U/L (109–245)	1729	212 (170, 292)	211 (170, 289)	252 (196, 391)	<0.001
Ferritin, ng/ml (4.6–204)	308	567 (246, 1218)	553 (242, 1209)	817 (323, 1599)	0.119
Coagulation co-variates					
aPTT, s (28–43.5)	1356	34 (30, 38)	34 (30, 38)	35 (32, 40)	0.009
Fibrinogen, g/L (2–4)	1323	3.7 (2.9, 4.6)	3.7 (2.9, 4.6)	3.8 (3.4, 4.6)	0.222
D-dimer, mg/L (<0.5)	1602	0.4 (0.2, 1.1)	0.4 (0.2, 1.0)	0.6 (0.2, 4.0)	0.043
Biochemistry co-variates					
ALT, U/L (5–35)	1832	38 (22, 67)	38 (22, 67)	36 (24, 67)	0.882
AST, U/L (8–40)	1830	32 (22, 49)	32 (22, 49)	35 (27, 58)	0.039
Total bilirubin, μmol/L (5.1–19)	1586	14 (10, 19)	14 (10, 19)	15 (11, 29)	0.069
Creatine kinase, U/L (26–140)	1493	88 (54, 165)	88 (54, 163)	102 (52, 282)	0.164
BNP, pg/ml (<100)	838	61 (18, 242)	60 (17, 238)	85 (30, 679)	0.042
Myoglobin, ng/ml (<140)	972	35 (21, 73)	34 (21, 71)	41 (31, 303)	0.004
Troponin I, ng/L (<26.2)	1083	4 (1, 14)	4 (1, 14)	8 (3, 34)	0.006
BUN, mmol/L (2.9–8.2)	1815	4.9 (3.9, 6.7)	4.9 (3.9, 6.7)	5.3 (3.8, 9.9)	0.255
Scr, μmol/L (44–106)	1813	71 (59, 85)	71 (60, 85)	65 (55, 82)	0.076
Lymphocyte subsets					
CD3+, (58–84%)	759	71 (62, 78)	72 (62, 78)	68 (58, 82)	0.877
CD4+, (25–51%)	759	41 (32, 48)	41 (33, 48)	39 (29, 49)	0.373
CD8+, (14–39%)	759	23 (17, 30)	23 (17, 30)	21 (17, 32)	0.793
NK-cells (3–30%)	561	10 (6, 16)	10 (6, 16)	8 (5, 18)	0.688
B-cells (4–18%)	561	12.6 (8.6, 18)	12.7 (8.7, 18)	12.6 (6.2, 19.3)	0.828
CD4+/CD8+ ratio (0.41–2.72)	755	1.9 (1.4, 2.7)	1.9 (1.4, 2.7)	2.1 (1.4, 3.1)	0.462
Cytokines					
IL-4, pg/ml (0.1–3.2)	505	3 (2, 4)	3 (2, 4)	2 (1, 3)	0.32
IL-6, pg/ml (0.1–2.9)	857	10 (4, 42)	10 (4, 42)	17 (7, 102)	0.085
IL-10, pg/ml (0.1–5)	505	4 (3, 6)	4.3 (2.9, 5.6)	4.4 (2.7, 7.9)	0.642
TNF-α, pg/ml (0.1–23)	505	3.3 (2.2, 5.4)	3.4 (2.2, 5.5)	2.9 (1.8, 3.5)	0.029
IFN-γ, pg/ml (0.1–18)	505	3.1 (2.0, 4.1)	3.1 (2.0, 4.1)	2.7 (1.8, 4.0)	0.447

Data are median (IQR).

NLR neutrophil-to-lymphocyte ratio, *CRP* c-reactive protein, *LDH* lactate dehydrogenase, *aPTT* activated partial thromboplastin time, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *BNP* B-type natriuretic peptide, *BUN* blood urea nitrogen, *Scr* serum creatinine, *IL* interleukin, *TNF* tumor necrosis factor, *IFN* interferon.

versus 13 mg/L [IQR 3–49 mg/L]; $P = 0.047$), procalcitonin (0.1 ng/ml [IQR 0.06–0.2 ng/ml] versus 0.05 ng/ml [IQR 0.05–0.1 ng/ml]; $P = 0.001$), and D-dimer (0.6 mg/L [IQR 0.2–4.0 mg/L] versus 0.4 mg/L [IQR 0.2–1.0 mg/L]; $P = 0.043$) and longer activated partial thromboplastin time (aPTT, median 35 s [IQR 32–40 s] versus 34 s [IQR 30–38 s]; $P = 0.009$). No significant difference was found in serum concentrations of ferritin or fibrinogen.

Cancer subjects had higher median activities of lactate dehydrogenase (LDH) (252 U/L [IQR 196–391 U/L] versus 211 U/L [IQR 170–289 U/L]; $P < 0.001$), aspartate aminotransferase (AST, 35 U/L [27–58 U/L] versus 32 U/L [22–49 U/L]; $P = 0.039$), concentrations of B-type natriuretic peptide (BNP, 85 pg/ml [30–679 pg/ml] versus 60 pg/ml [17–238 pg/ml]; $P = 0.042$), myoglobin (41 ng/ml [31–303 ng/ml] versus 34 ng/ml [21–71 ng/ml]; $P = 0.004$) and troponin I (8 ng/L [3–34 ng/L] versus 4 ng/L [1–14 ng/L]; $P = 0.006$). There were no significant differences in activities of alanine aminotransferase (ALT) or creatine kinase or concentrations of total bilirubin, blood urea nitrogen (BUN) or serum creatinine (Scr).

Complications and outcomes of subjects with cancer and without cancer

As shown in Table 3, subjects with cancer had higher incidence of ARDS (19 [29%] versus 208 [12%]; $P < 0.001$), bacterial infection (30 [46%] versus 533 [30%]; $P = 0.005$),

Table 3 Complications and therapy.

	Total $N = 1859$	Non-cancer $N = 1794$	Cancer $N = 65$	P-value
Complications				
ARDS	227 (12)	208 (12)	19	<0.001
Bacterial infections	563 (30)	533 (30)	30	0.005
Septic shock	64 (4)	57 (4)	7	0.007
Acute kidney injury	99 (5)	90 (5)	9	0.002
Heart injury	229 (12)	215 (12)	14	0.021
Abnormal LFT	456 (25)	440 (25)	16	0.984
Gastro-intestinal bleeding	34 (2)	29 (2)	5	<0.001
Coagulopathy	49 (3)	47 (3)	2	0.821
Multiple organ failure	129 (7)	117 (7)	12	<0.001
Therapy				
Antibiotics	1559 (85)	1497 (85)	62	0.019
Anti-fungal drugs	71 (4)	64 (4)	7	0.005
Oseltamivir	757 (41)	729 (41)	28	0.697
Umifenovir	1386 (75)	1343 (75)	43	0.110
Lopinavir/ritonavir	339 (23)	328 (24)	11	0.357
Interferon alpha	387 (21)	363 (20)	24	0.001
Corticosteroids	753 (41)	725 (40)	28	0.670
IVIG	506 (29)	478 (29)	28	0.009
High-flow nasal cannula oxygen therapy	233 (16)	214 (15)	19	0.001
Non-invasive mechanical ventilation	145 (8)	130 (7)	15	<0.001
Invasive mechanical ventilation	85 (5)	78 (4)	7	0.015
ECMO	4 (0.2)	4 (0.2)	0	>0.999
CRRT	23 (1)	22 (1)	1	0.561
Outcomes				
Death	209 (11)	191 (11)	18	<0.001
Time from illness onset to ICU admission, median (IQR), days	14 (10, 20)	14 (10, 20)	14 (7, 21)	0.790
Time from illness onset to repeated negative SARS-CoV-2 tests, median (IQR), days	22 (17, 28)	22 (17, 28)	20 (16, 28)	0.379
Time from illness onset to admission, median (IQR), days	10 (7, 15)	10 (7, 15)	10 (7, 13)	0.104
Time from illness onset to progression, median (IQR), days	10 (7, 15)	10 (5, 14)	11 (6, 18)	0.284
Time from illness onset to outcome[a], median (IQR), days	30 (23, 37)	30 (23, 37)	28 (21, 35)	0.209
Time from diagnosis to outcome[a], median (IQR), days	19 (13, 27)	19 (13, 27)	21 (14, 27)	0.503
Time from admission to outcome[a], median (IQR), days	18 (12, 23)	18 (12, 23)	18 (13, 26)	0.353

LFT liver function test, *ARDS* acute respiratory distress syndrome, *IVIG* intravenous immunoglobin, *ECMO* extra-corporeal membrane oxygenation, *CRRT* continuous renal replacement therapy, *ICU* intensive care unit.

[a]Outcome refers to discharged alive or died.

septic shock (7 [11%] versus 57 [4%], $P = 0.007$), acute kidney injury (9 [14%] versus 90 [5%]; $P = 0.002$), cardiac injury (14 [22%] versus 215 [12%]; $P = 0.021$), gastrointestinal bleeding (5 [8%] versus 29 [2%]; $P < 0.001$) and multiple organ failure (12 [19%] versus 117 [7%]; $P < 0.001$).

Subjects with cancer were also more likely to receive antibiotics (62 [95%] versus 1497 [85%]; $P = 0.019$), antifungal drugs (7 [11%] versus 64 [4%]; $P = 0.005$), intratracheal α-interferon (24 [37%] versus 363 [20%]; $P = 0.001$), immunoglobin intravenous (IVIG, 28 [44%] versus 478 [29%]; $P = 0.009$), high-flow nasal cannula oxygen (19 [31%] versus 214 [15%]; $P = 0.001$), invasive (7 [11%] versus 78 [4%]; $P = 0.015$) and non-invasive (15 [23%] versus 130 [7%]; $P < 0.001$) mechanical ventilation. There was no significant difference in use of extra-corporeal membrane oxygenation (ECMO) or continuous renal replacement therapy (CRRT).

Subjects with cancer were more likely to die from COVID-19 (18 [28%] versus 191 [11%]; $P < 0.001$). There were no significant differences in interval from hospital admission to ICU admission, repeatedly negative SARS-CoV-2 tests, interval from admission to recovery, COVID-19 progression or death.

Multi-variable analyses

We analyzed co-variates associated with risk of in-hospital death from COVID-19 in a Cox regression model including co-variates with $P < 0.05$ in uni-variable analyses excluding those with co-linearity (Supplement Table 2). Age *per* year increase (HR = 1.05 [1.04, 1.07]; $P < 0.001$), male (HR = 1.53 [1.09, 2.14]; $P = 0.013$), admission COVID-19 severity severe/critical (HR = 28.2 [13.8, 57.6]; $P < 0.001$), current smoking (HR 2.00 [1.10, 3.66]; $P = 0.024$), admission temperature *per* °C (HR = 1.24 [1.03, 1.50]; $P = 0.026$), platelet concentration *per* 10 E + 9/L increase (HR = 0.996 [0.994, 0.998]; $P = 0.001$) and plasma D-dimer concentration *per* mg/L increase (HR = 1.04 [1.02, 1.05]; $P < 0.001$) but not having cancer (HR = 1.59 [0.95,

2.69]; $P = 0.081$; Table 4) were significantly associated with risk of in-hospital death from COVID-19.

Next, we performed separate multi-variable regression analyses in subjects < and ≥65 years after adjusting age and sex. We found having cancer was significantly associated with risk of in-hospital death from COVID-19 in subjects <65 years (HR = 2.45 [1.04, 5.76]; $P = 0.041$) but not in subjects ≥65 years (HR = 1.12 [0.56, 2.24]; $P = 0.740$). Other risk factors in subjects <65 years included age per year increase (HR = 1.05 [1.02, 1.09]; $P = 0.001$, COVID-19 severity severe/critical at admission (HR = 16.1 [6.3, 40.8]; $P < 0.001$) and plasma D-dimer concentration per mg/L increase (HR = 1.21 [1.08, 1.17]; $P < 0.001$). In subjects ≥65 years age per year increase (HR 1.05 [1.02, 1.07]; $P < 0.001$), admission COVID-19 severity severe/critical (HR = 46.1 [14.6, 145.9]; $P < 0.001$), platelet concentration *per* 10 E + 9/L increase (HR = 0.996 [0.993-0.998]; $P = 0.002$) and plasma D-dimer concentration *per* mg/L increase (HR 1.03 [1.01, 1.04]; $P < 0.001$) were correlated with risk of in-hospital death from COVID-19.

Comparison of co-variates in subjects with cancer living or dying from COVID-19

18 subjects with cancer died. There was no difference in median age (68 years, IQR 56–78 years versus 62 years, IQR 51–67 years; $P = 0.146$, Supplement Table 3), sex ($P = 0.58$) or frequencies of prior co-morbidities between non-survivors and survivors. Non-survivors were more likely to have had shortness of breath on admission (78% versus 36%; $P = 0.005$) but there were no significant differences in other signs or symptoms on admission or in findings on lung CT scan. Non-survivors were more likely to have had severe/ critical COVID-19 on admission than survivors (94% versus 38%, $P < 0.001$). Non-survivors had significantly higher median concentrations/activities of neutrophils, CRP, procalcitonin, LDH, ferritin, D-dimer, ALT, AST, total bilirubin, creatine kinase, BNP, myoglobin, troponin I, BUN, Scr, and NLR, and lower

Table 4 Multi-variable analyses of co-variates associated with in-hospital death of persons with cancer.

	All		<65 years		≥65 years	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age, years	1.05 (1.04, 1.07)	<0.001	1.05 (1.02, 1.09)	0.001	1.05 (1.02, 1.07)	<0.001
Male	1.53 (1.09, 2.14)	0.013	1.82 (0.999, 3.30)	0.050	1.50 (0.998, 2.27)	0.051
Severity (severe/critical)	28.17 (13.78, 57.62)	<0.001	16.06 (6.32, 40.80)	<0.001	46.10 (14.56, 145.91)	<0.001
Cancer	1.59 (0.95, 2.69)	0.081	2.45 (1.04, 5.76)	0.041	1.12 (0.56, 2.24)	0.740
Current smoking	2.00 (1.10, 3.66)	0.024	1.22 (0.37, 4.02)	0.741	2.43 (1.20, 4.91)	0.014
Temperature at admission (°C)	1.24 (1.03, 1.50)	0.026	1.09 (0.79, 1.50)	0.609	1.35 (1.05, 1.73)	0.021
Platelets x10E + 9/L	0.996 (0.994, 0.998)	0.001	0.997 (0.994, 1.001)	0.099	0.996 (0.993, 0.998)	0.002
D-dimer, mg/L	1.04 (1.02, 1.05)	<0.001	1.21 (1.08, 1.17)	<0.001	1.03 (1.01, 1.04)	<0.001

concentrations of lymphocytes (Supplement Table 4). Percentages of CD3-, CD4- and CD8-positive T-cells, CD4/CD8 ratio and B-cells were similar between survivors and non-survivors. In contrast, percentage of natural killer (NK)-cells was significantly lower in non-survivors (4% [IQR 2–6%] versus 14% [IQR 7-18%]; $P = 0.008$). Non-survivors had higher concentrations of IL-6 (287 pg/ml [IQR 22–686 pg/ml] versus 12 pg/ml [IQR 5–27 pg/ml]; $P = 0.001$) and IL-10 (10 pg/ml [IQR 4–18 pg/ml] versus 4 pg/ml [IQR 3–5 pg/ml]; $P = 0.012$). There was no significant difference in serum concentrations of IL-4, TNF-α or IFN-γ. Time from admission to recovery, discharge or death was significantly shorter in non-survivors (21 days [IQR 15–30 days] versus 31 days [IQR 24–37 days]; $P = 0.002$; Supplement Table 5).

We further compared co-variates between subjects with solid and hematological cancers (Supplement Table 6). Subjects with hematological cancer were more likely to be young (39 years [IQR 23–66 years] versus 63 years [IQR 57–69 years]; $P = 0.019$), to have lower hemoglobin concentration (92 g/L [IQR 86–116 g/L] versus 121 g/L [IQR 106–133 g/L]; $P = 0.011$) and longer aPTT (42 s [IQR 38–48 s] versus 35 s [IQR 32–38 s]; $P = 0.001$). There was no difference in other co-variates including signs and symptoms, laboratory co-variates or co-morbidities on admission. Rates of ICU admission bacterial co-infections, of ARDS and of in-hospital death from COVID-19 (2/9 versus 14/50; $P > 0.999$) were similar. We also compared co-variates in subjects in complete remission or not. (Supplement Table 7) Subjects not in complete remission were more likely to be young (54 years [IQR 27-66 years] versus 63 years [IQR 58–71 years]; $P = 0.034$), to have a lower incidence of diabetes and lower median concentrations of hemoglobin (100 g/L [IQR 89–107 g/L] versus 129 g/L [IQR 118–137 g/L]; $P < 0.001$) and plasma IL-6 (43 pg/ml [13–593 pg/ml] versus 11 pg/ml [3–37 pg/ml]; $P = 0.022$) and a higher risk of death (9/18 versus 7/41; $P = 0.013$).

Discussion

There is controversy whether having cancer is associated with an increased risk of death from COVID-19. Some studies report an association [1–3, 5–9, 13–18], others not [19–26]. These differences could be related to cancer patients' age or other factors. We studied 1859 consecutive subjects with COVID-19, 65 of whom also had cancer. Detailed data were available in 59. The strongest risk factor for in-hospital death from COVID-19 in all subjects and in subjects with cancer was COVID-19 severity on admission. However, we also found having cancer increased risk of in-hospital death from COVID-19 in subjects <65 years but not in those ≥65 years. We also found risk of death in

persons with cancer only operated in those <65 years and in those not in complete remission. Type of cancer (solid or hematological) was not significantly correlated with risk of in-hospital death from COVID-19.

There are limitations to our study. It was retrospective, has relatively few subjects with cancer but >1800 controls and lacks a validation cohort. Nevertheless, we think our data may be informative in treating persons with cancer and COVID-19.

Data availability

All data are included in the typescript and supplement.

Author contributions YH and QL designed the study. Lei Chen, Q Li, WH, JY, Li Chen, YC, WC, DW, FD, LC, QR, LL, QL, WR, FG, HW, and ZC collected the data. All authors had full access to the data, were involved in data interpretation and vouch for the accuracy of the analyses. QL, Lei Chen, and RPG prepared the typescript which all authors approved and agreed to submit for publication.

Compliance with ethical standards

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