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Coronary Calcifications on Non-Gated Chest CT in COVID-19 Patients: Prevalence and Impact on Outcomes

Calcificações Coronárias em TC do Tórax em Doentes COVID-19: Prevalência e Impacto Clínico

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Abstract

Introduction: Recent studies have demonstrated the complex interplay between COVID-19 infection, cardiovascular disease, and poor outcomes. In this context, the evaluation of coronary artery calcifications (CAC) may provide additional risk stratification in COVID-19 patients.
Methods: We retrospectively enrolled 105 consecutive COVID-19 patients who underwent non-gated chest CT at our department from April to July 2020. CAC were assessed by two independent observers and graded as absent, mild, moderate, and severe. Clinical files were checked for basic demographic variables, C-reactive protein at admission, number of hospitalization days, need for ventilatory support and death. Original CT reports were checked for mention of CAC.
Results: Sixty-six patients had CAC on chest CT. Patients with any CAC were more likely to need ventilatory support (OR: 3.6) and to die (OR: 8.9). Patients with severe CAC were more likely to need ventilatory support (OR: 4.1) and with moderate CAC more likely to die (OR: 11.1). Patients with CAC had longer hospitalizations (mean: 18.5 days) than patients without CAC (mean: 12.4 days, p=0.038). Original radiological reports included CAC in only 22 (21%) of patients, but 12 (52.2%) of the severe CAC were included in the report.
Conclusion: CAC are associated with a worse prognosis in COVID patients and may be used as an additional risk stratification tool in this patient population. CAC should be reported whenever visible.

Keywords

COVID-19; CT scan; Cardiovascular diseases.

Resumo

Introdução: Estudos recentes demonstraram a relação complexa entre infeção por COVID-19, doença cardiovascular e mau prognóstico. Neste contexto, a avaliação das calcificações das artérias coronárias (CAC) pode ser uma ferramenta adicional na estratificação do risco clínico destes doentes.
Métodos: Neste estudo retrospetivo foram recrutados 105 doentes consecutivos infetados com COVID-19, que realizaram TC do tórax sem gating cardíaco, numa única instituição entre Abril e Julho de 2020. As CAC foram avaliadas por dois observadores independentes e classificadas como ausentes, ligeiras, moderadas ou severas. O processo clínico dos doentes foi consultado para informação sobre variáveis demográficas, proteína C reativa à admissão, número de dias hospitalizado, necessidade de suporte ventilatório e morte. Os relatórios originais das TC foram consultados para verificar se mencionavam a presença de CAC.
Resultados: Sessenta e seis (63%) dos doentes avaliados apresentavam CAC na TC. Doentes com qualquer grau de CAC tiveram maior probabilidade de precisar de suporte ventilatório (OR: 3,6) e de morrer (OR: 8,9). Doentes com CAC severas tiveram maior probabilidade de precisar de suporte ventilatório (OR: 4,1), e com CAC moderadas maior probabilidade de morrer (OR: 11,1). Doentes com CAC estiveram internados durante mais tempo (p=0,038). Apenas 21% dos relatórios originais (22 doentes) incluíram informação sobre CAC, mas estas foram mencionadas em 52% (12 doentes) dos relatórios dos doentes com CAC severas.
Conclusão: As CAC estão associadas a pior prognóstico em doentes infetados com COVID-19, e podem ser usadas como uma ferramenta adicional na estratificação do risco clínico destes doentes. As CAC devem ser incluídas no relatório do radiologista sempre que observadas.

Palavras-chave

COVID-19; TC; Doenças cardiovasculares.

Introduction

Cardiovascular diseases are the most common cause of death worldwide, particularly in Europe.[1] In Portugal, cardiovascular diseases accounted for 29.4% of total mortality in 2017.[2] Interventions targeting modifiable risk factors and preventive drug therapies reduce future cardiovascular events. Hence, early diagnosis of cardiovascular diseases has the potential to reduce future morbidity and mortality.

Coronary artery calcifications (CAC) are associated with increased number of major adverse cardiovascular events (MACE), both in symptomatic and asymptomatic patients, and are considered an atherosclerosis biomarker.[3] Current guidelines recommend CAC scoring as a tool to reclassify cardiovascular risk upwards and downwards in addition to conventional risk factors.[4]

Cardiovascular (CV) diseases are associated with worse prognosis in COVID-19 patients. Conversely, COVID-19 patients with pre-existing CV diseases are at increased risk of conversion from an asymptomatic subclinical state to unstable disease, with plaque instability and higher risk of acute coronary syndrome.[5,6,7]

In this study we assess the association between visual CAC scoring on non-gated chest CT examinations of COVID-19 patients and clinical outcomes. In addition, we evaluate the report rate of CAC in this population.

Methods

Population:

We prospectively enrolled 105 consecutive RT-PCR COVID-19 positive patients who underwent an ungated chest CT, between April and July 2020. Clinical files were checked for C-reactive protein (CRP) at admission and number of hospitalized days. Clinical endpoints were ventilatory support (invasive and non-invasive) and mortality. Two patients were not hospitalized and were excluded from the clinical endpoint analysis. Taking in account the observational and retrospective nature of this study, the need for informed consent was waived by the ethics committee.

Image analysis:

The presence of coronary calcifications was evaluated by two independent observers – observer 1, a radiologist with 8 years of experience in thoracic imaging, and observer 2, with 3 years of experience in thoracic imaging. CAC were scored using a simple visual ordinal score on a whole patient basis, as described in the BSCCT/BSTI guidelines, using the categories absent, mild, moderate, and severe (figure 1). Discordant cases were solved by simple consensus. The Kappa coefficient of Cohen was used to calculate the interobserver variability. The original exam reports were reviewed for the mention of CAC.

Statistical analysis:

The following statistical tests were used:

- T-test: compare the age means in relation to ventilatory support and death;
- Chi-square: compare gender differences and presence of CAC across the outcomes;
- Mann-Whitney U test: compare CAC scores across the outcomes; difference in CRP values and presence of CAC; difference in hospitalized days and presence of CAC (in patients who survived).

Univariable logistic regression was used to calculate the odds ratio (OR) of needing ventilatory support and death in relation to the presence of CAC.

Statistical significance was defined at 0.05 (two-tailed). Statistical analysis was performed using SPSS 27 (IBM).

Results

The basic demographic and clinical variables, presence of CAC and CAC scores according to the clinical endpoints (ventilatory support and death) are presented in table 1. The age range was 20-98 years (65.2 ± 16.6, mean ± standard deviation). There was a small male predilection with 54 (52.4%) males and 49 (47.6%) females.

The median hospitalization time was 12 days (IQR: 13 days), ranging from 2 to 82 days. The mean CRP at admission was 77.9 mg/dL (± 86.2 mg/dL).

A total of 33 (32%) of patients needed ventilatory support and 14 (13.6%) died.

Sixty-six patients had CAC on chest CT.

CAC scoring and reporting:

The Kappa coefficient of Cohen for the two observers was 0.72 (standard-error: 0.054). After application of the simple consensus method, 39 (37.1%) patients were classified as having no CAC (absent), 30 (28.6%) as mild, 13 (12.4%) as moderate and 23 (21.9%) as severe (table 2).

The original report rates of CAC according to the different CAC scores are shown in table 3. CAC were reported in 22 (21%) of the original reports and in 21 (31.8%) of the patients classified as having CAC. Report rates were higher for patients with severe calcifications (52.2%) compared to mild calcifications (13.3%) ($p<0.001$).

CAC and clinical endpoints:

Univariable logistic regression results are shown in table 4. Patients with CAC had an OR of 3.6 ($p=0.012$) of needing ventilatory support and 8.9 ($p=0.039$) of death.

In patients who survived, hospitalization days were higher if they had CAC ($p = 0.038$). There was not a statistically significant difference in CRP values at admission in relation to CAC (table 5).

Discussion

Imaging indications in COVID-19 patients are controversial and may vary according to country and resource availability. A multinational statement by the Fleischer society recommends chest imaging in patients with COVID-19 and worsening respiratory status and in patients with moderate to severe clinical features of disease and high pre-test probability.[8] In this way, chest CT is not only an important tool for diagnosis and severity grading, but also to assess extra-pulmonary manifestations.[7] In fact, our study showed the presence of CAC was associated with worse patient prognosis, particularly by increasing the risk of ventilatory support (OR: 3.6), number of hospitalized days (12.4 days vs 18.5 days) and death (OR: 8.9). Although statistical significance was not achieved, there was also a tendency for higher CRP values in patients with CAC (92.3 mg/dL vs 52.1 mg/dL). Recently published studies have achieved similar results[9,10,11] and support the role of CAC as an imaging biomarker for adverse clinical outcomes in COVID-19 patients.

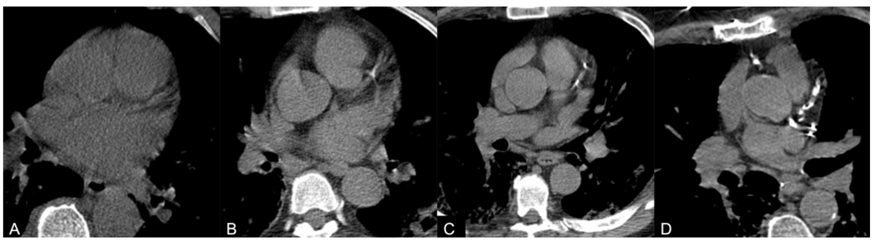

Figure 1 – Axial non-gated CT of four different patients exemplifying the CAC score. A – no calcifications. B – mild calcifications. C – moderate calcifications. D – severe calcifications.

Table 1 – Basic clinical variables, presence of CAC and CAC score acording to the clinical endpoints (need for ventilatory support and death). Statistically significant differences are marked in bold.

		Admitted patients (n = 103)	Ventilatory support			Death		
			No	Yes	p-value	No	Yes	p-value
Age (mean ± SD)		65.1 ± 1.7	63.5 ± 18.5	68.6 ± 12	0.087	63.9 ± 17.1	72.9 ± 12	0.058
Gender (n, %)	Female	49 (47.6%)	36 (73.5%)	13 (26.5%)	0..254	46 (93.9%)	3 (6.1%)	**0,035**
	Male	54 (52.4%)	34 (63%)	20 (37%)		43 (79.6%)	11 (20.4%)	
CRP (mean ± SD)		79.9 ± 86.2	58.3 ± 72.2	118.4 ± 99	**<0.001**	69.6 ± 77.3	129.9 ± 119.3	**0.025**
N hospitalized days (mean ± SD)		15.8 ± 13.8	12.4 ± 9.6	23.2 ± 18.2	**<0.001**	N/A		0.817
Presence of CAC (n, %)	No	37 (35.9%)	31 (83.8%)	6 (16.2%)	**0..010**	36 (97.3%)	1 (2.7%)	**0.015**
	Yes	66 (64.1%)	39 (59.1%)	27 (40.9%)		53 (80.3%)	13 (19.7%)	
CAC score (n, %)	Absent	37 (35.9%)	31 (83.8%)	6 (16.2%)	**0..035**	36 (97.3%)	1 (2.7%)	**0.043**
	Mild	30 (29.1%)	16 (53.3%)	14 (46.7%)		24 (80%)	6 (20%)	
	Moderate	13 (12.6%)	10 (76.9%)	3 (23.1%)		10 (76.9%)	3 (23.1%)	
	Severe	23 (22.3%)	13 (56.5%)	10 (43.,5%)		19 (82.6%)	4 (17.4%)	

Table 2 – Interobserver variability of CAC score and results after simple consensus.

Interobserver variability for CAC score			
	Observer 1	Observer 2	Final
	N (%)	N (%)	N (%)
Absent	34 (32.4)	40 (38.1)	39 (37.1)
Present	71 (67.6)	55 (61.9)	66 (62.9)
• Mild	36 (34.3)	32 (30.5)	30 (28.6)
• Moderate	16 (15.1)	11 (10.5)	13 (12.4)
• Severe	19 (17.9)	22 (21)	23 (21.9)
Total	105 (100)	105 (100)	105 (100)

Table 3 – Original CAC report rates in relation to CAC scores.

CAC score/ CAC included in the original report		
	No	Yes
	N (%)	N (%)
Absent	38 (97.4)	1 (2.6)
Present	45 (68.2)	21 (31.8)
• Mild	26 (86.7)	4 (13.3)
• Moderate	8 (61.5)	5 (38.5)
• Severe	11 (47.8)	12 (52.2)
Total	83 (79)	22 (21)

Table 4 – Univariable logistic regression showing the OR for ventilatory support and death in relation to presence of CAC. Significant OR are flagged in bold.

	Ventilatory support		Death	
	OR [95% CI]	p	OR [95% CI]	p
Presence of CAC	**3.6 [1.3-9.8]**	**0.012**	**8.9 [1.1-71.1]**	**0.039**

Table 5 – Difference in CRP values and hospitalization days in relation to the presence of CAC. Significant differences are flagged in bold.

Presence of CAC	CRP (mg/dL)		N Days Hospitalized	
	mean ± SD	p value	mean ± SD	p value
No	52.1 ± 52.1	0.057	12.4 ± 10.3	**0.038**
Yes	92.3 ± 97.7		18.5 ± 15.9	

Although the importance of traditional CV risk factors cannot be overemphasized, current evidence shows a significantly increased risk of myocardial infarction in the short, medium and long-term for patients with acute bacterial and viral infections.[12] In the particular case of COVID-19 infection, three main mechanisms have been described that justify worse CV outcomes[7] – multi-organ failure and consequent cardiac injury secondary to severe hypoxia caused by the respiratory syndrome; endothelial dysfunction and myocardium damage due to ACE2 binding; activation of the inflammatory cascade and subsequent cytokine storm. Cardiovascular complications of COVID-19 infection have been extensively described in the literature, and include myocarditis, acute myocardial infarction, heart failure and cardiac arrithmyas.[6,13,14,15] Conversely, patients with chronic CV diseases like ischemic heart disease or heart failure are known to have worse prognosis when infected with COVD-19.[16,17]

The association between CAC and cardiovascular CV disease is well established. During the National Lung Cancer Screening Trial, the hazard ratio (HR) for coronary disease death was 2.09 in the patients with mild, 3.86 with moderate and 6.95 with severe calcifications, when compared to the absence of calcifications.[18] Also, the visual scoring of CAC was found to be a predictor of all-cause and CV mortality, independent of smoking status.[19] Visual grading and assessment of CAC is therefore recommended by the SCCT[20] and BSTI[3] guidelines in all chest CT due to its simplicity, good interobserver variability and correlation with Agatson score. In our study, visual grading of the CAC was reproducible, with a substantial Kappa coefficient (0.72), concordant with the results reported in the literature.[18]

Thus, visual CAC scoring is a simple and reliable method to provide additional prognostication in COVD-19 patients, available in all patients undergoing chest CT and not requiring additional image post-processing. In addition, it may provide the first indication of coronary artery disease presence.

In our cohort, only 21% of the original reports included information about CAC. However, considering only the patients with CAC, 31.8% were mentioned in the original report, suggesting that denial by omission may have occurred. Previous studies reported similar results – one study in 2013 found that CAC was recorded in the radiologist report of non-contrast chest CT exams in only 44% of the patients with CAC;[21] another study in 2015 found unreported potentially relevant cardiovascular findings in 39.6% of patients undergoing chest CT for pulmonary interstitial disease, lung cancer staging or PE assessment.[22]

Our recommendation is to report CAC in all chest CT examinations, whenever they are visible. Specific indications for different CAC grades are currently not defined, and therefore the most important attitude is to report their presence.

Clinical implications of the reported findings were not evaluated, and most physicians may be unaware of the importance of these findings. A recent study found that only 5% of patients with reported CAC on non-gated chest CT had their regular prescription changed.[23] Nevertheless, the report rate of CAC was low. CT scans of COVID-19 patients were all acquired in the emergency setting. We do not know if in a different setting the result would have been different.

Our study has limitations. First, its retrospective single center nature. Age correction was not performed, and CAC is known to be strongly associated with age. However, age was not statically different in patients who needed ventilatory support, ICU admission or died.

Also, patients with previously known coronary disease were not excluded, which may have introduced an outcome bias as these patients may already be under treatment.

Finally, lung parenchyma involvement by COVID-19 was not considered is this study. A previous study developed an artificial neural network to estimate COVID-19 disease severity, which showed correlation with clinical outcomes.[24,25] In the future, it would be interesting to incorporate CAC information in this algorithm to further stratify and improve prognostication of COVID-19 patients.

Conclusion

In conclusion, CAC are associated with worse prognosis in COVID-19 patients and can be used as a biomarker for adverse clinical outcomes. Radiologists should be aware of the importance of this finding and record it on every chest CT examination when present.

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Ethical disclosures / Divulgações Éticas

Conflicts of interest: The authors have no conflicts of interest to declare.
Conflitos de interesse: Os autores declaram não possuir conflitos de interesse.
Confidentiality of data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.
Confidencialidade dos dados: Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação dos dados de doentes.
Protection of human and animal subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).
Protecção de pessoas e animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.

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