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Original article

Imaging strategies used in emergency departments for the diagnostic workup of COVID-19 patients during the first wave of the pandemic: a multicenter retrospective cost-effectiveness analysis

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ABSTRACT

Objectives: Emergency departments (EDs) were on the front line for the diagnostic workup of patients with COVID-19–like symptoms during the first wave. Chest imaging was the key to rapidly identifying COVID-19 before administering RT-PCR, which was time-consuming. The objective of our study was to compare the costs and organizational benefits of triage strategies in ED during the first wave of the COVID-19 pandemic.
Methods: We conducted a retrospective study in five EDs in France, involving 3712 consecutive patients consulting with COVID-like symptoms between 9 March 2020 and 8 April 2020, to assess the cost effectiveness of imaging strategies (chest radiography, chest computed tomography (CT) scan in the presence of respiratory symptoms, systematic ultra–low-dose (ULD) chest CT, and no systematic imaging) on ED length of stay (LOS) in the ED and on hospital costs. The incremental cost-effectiveness ratio was calculated as the difference in costs divided by the difference in LOS.
Results: Compared with chest radiography, workup with systematic ULD chest CT was the more cost-effective strategy (average LOS of 6.89 hours; average cost of €3646), allowing for an almost 4-hour decrease in LOS in the ED at a cost increase of €98 per patient. Chest radiography (extendedly dominated) and RT-PCR with no systematic imaging were the least effective strategies, with an average LOS of 10.8 hours. The strategy of chest CT in the presence of respiratory symptoms was more effective than the systematic ULD chest CT strategy, with the former providing a gain of 37 minutes at an extra cost of €718.

Abbreviations: CT, computed tomography; ED, emergency departments; COPD, chronic obstructive pulmonary disease; HBP, high blood pressure; ULD, ultra low dose; ICER, incremental cost effectiveness ratio; LOS, length of stay; WTP, willingness to pay.

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Discussion: Systematic ULD chest CT for patients with COVID-like symptoms in the ED is a cost-effective strategy and should be considered to improve the management of patients in the ED during the pandemic, given the need to triage patients. **Sabrina Kepka, Clin Microbiol Infect 2022;■:1**
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Introduction

Around the world, there have been 308 million cumulative cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), with 5.4 million cumulative deaths [1]. The first wave of the pandemic challenged healthcare systems, especially in Europe [2].

Emergency departments (EDs) were on the front line for the diagnostic workup for COVID-19. An inefficient triage strategy significantly affected the quality of care in the ED [3]. In this specific context, hospitals have established empirical diagnostic procedures. RT-PCR has been used from the outset as the diagnostic reference standard; however, it is time consuming, especially in the beginning of the pandemic. Indeed, the diagnostic workup in the ED conditioned the transfer to an appropriate medical ward and the long RT-PCR results were not adapted to the need for rapid triage. A shorter diagnostic time would facilitate faster decision making, thus optimizing ED patient flow [4].

The WHO recommend using chest imaging for the diagnostic workup of COVID-19 when RT-PCR is unavailable or when results are delayed [5]. During the first wave, before the availability of rapid antigen testing, chest imaging was the key to rapidly identifying COVID-19 [6]. Compared to computed tomography [CT], chest radiography is a low-cost strategy for the diagnosis of COVID-19 [7], albeit with a lower sensitivity of 70% [8]. Chest CT has high specificity [9], between 83.5% to 96.2% (pooled specificity of 91.3% [95% CI, 87.6–94.0] in a Cochrane meta-analysis) compared with RT-PCR [10–12] and complement efficiently RT-PCR in diagnosing COVID-19, especially ultra–low-dose (ULD) CT [11].

To the best of our knowledge, no data exist on the costs and organizational benefits of diagnostic workup strategies in EDs that could inform decision makers in the event of a new infectious outbreak. Meta-analysis only identified eight studies concerning screening and diagnostic tests; interventions mainly concerned RT-PCR, and none concerned screening in EDs [13].

Our objective was to assess the cost-effectiveness of imaging strategies for triage of patients presenting with COVID-like symptoms in the ED during the first pandemic wave.

Methods

Study population, setting, and location

We conducted a retrospective study in the EDs of five university hospitals in France among 3712 consecutive patients aged over 18 years who consulted for COVID-like symptoms [14] between 9 March 2020 and 8 April 2020 (Fig. 1). Full methods are provided in the Supplementary materials, Appendix E1.

Comparators

We identified four strategies for the triage of patients with suspected COVID-19 in EDs: systematic chest radiography, chest CT in the presence of respiratory symptoms, systematic ULD chest CT, and no systematic imaging. Strategies could be performed in different centers and rapid RT-PCR could be performed for all strategies.

Perspective

Cost analysis was conducted from the hospital's perspective using hospital production costs or proxies (tariffs) when costs were not available.

Time horizon

The time horizon was 60 days after discharge from the hospital.

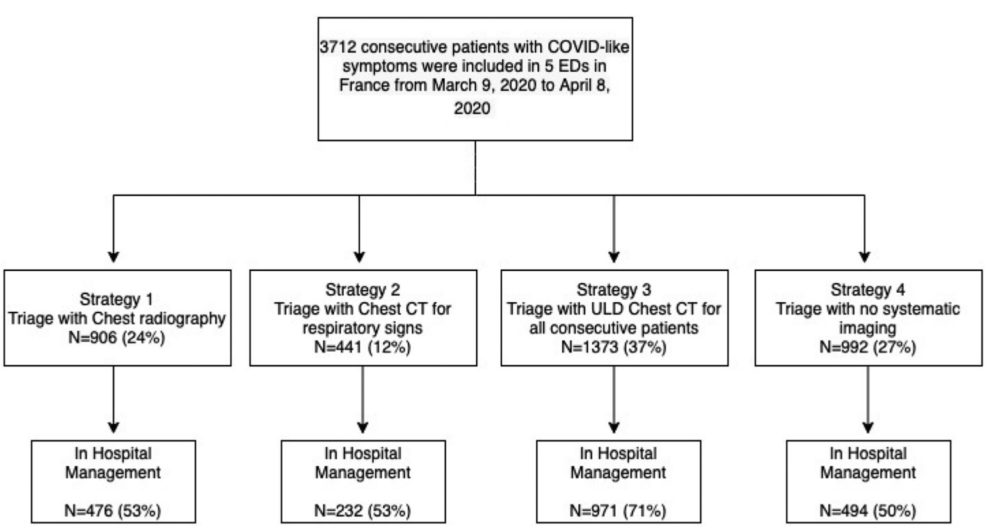

Fig. 1. Flowchart of the study conducted in the emergency departments of five University Hospitals in France during the first wave of COVID-19. ED, emergency department; ULD, ultra–low-dose.

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Discount rate

No discount rate was applied.

Selection, measurement, and valuation of outcomes

We evaluated the effect of the imaging strategy on LOS in the ED of patients presenting with COVID-like symptoms. The incremental cost-effectiveness ratio (ICER) was calculated as the difference in costs divided by the difference in LOS in the ED using the immediately less costly strategy. The choice of ED LOS as the outcome of interest (rather than diagnostic performance or clinical outcomes) was motivated by the COVID situation and the very large number of patients entering the ED for whom prompt decisions were needed to (1) initiate treatment if necessary, (2) and ensure that the risk of overcrowding was kept to a minimum, both for patients and for staff.

As secondary endpoints, we measured

1. Descriptive results of imaging in the ED, classified in four categories according to the European Society of Radiology and European Society of Thoracic Imaging guidelines: *consistent*, *indeterminate*, *other abnormalities*, and *no abnormalities* [13,15].
2. Care pathway after ED workup
3. Hospital LOS
4. Positive RT-PCR in the ED
5. Confirmed COVID-19 diagnosis in the ED according to RT-PCR and chest imaging results
6. Mortality at 60 days

Measurement and valuation of resources and costs

The following data for the economic evaluation were retrospectively collected: number and unit costs of chest CT and chest radiographs performed in EDs and costs of initial hospitalization and readmissions during the 60-day follow-up period.

Currency, price date, and conversion

Hospitalization and monitoring data were obtained from local hospitals' claims databases. Hospitalizations were evaluated using the corresponding French disease-related group (DRG) cost, adjusted by LOS, and number of days in the intensive care unit [16–18]. For patients who were not hospitalized, we imputed the average cost of outpatient visits in the ED, that is, €80, plus the cost of the imaging realized in the ED, valued using the statutory health insurance tariffs (see Supplementary material, Table S1).

Rationale and description of model

In order to compare the outcomes between the imaging strategies, we used a regression model weighted by inverse probability of the propensity score. For these variables' missing data, multiple imputation with chained equations was performed for each variable of the propensity score. We used a generalized linear model to model LOS in EDs and employed a Gaussian family with a log link, as the distribution of LOS in the ED was skewed and lower bounded to zero. For the costs, we used a generalized linear model with a gamma family with a log link.

Analytics and assumptions

We computed the groups' marginal effect and costs for comparison with the less costly strategy as a reference to obtain the average effect or cost increment.

Characterising uncertainty

The variability of the results was assessed using non-parametric bootstrapping, which provided multiple estimates of the ICER by randomly re-sampling the patient population 1000 times. The results are presented on the cost-effectiveness plane.

Characterising heterogeneity

We performed a deterministic sensitivity analysis to compare the more cost-effective strategy to the less costly strategy to examine the independent effect of the following variables and the ICER, substituting items of cost with five times the base case for each parameter.

Ethics approval, data, and safety monitoring

The study was approved by the ethics committee (CE 2021-141). In accordance with French legislation, formal written informed consent was not required for this type of study because data were entirely retrospectively studied [19].

Results

Of the 3721 patients included, the main strategy was “systematic ULD chest CT” ($n = 1373$; 37%). “No systematic imaging,” “chest radiography,” and “chest CT in the presence of respiratory symptoms” were performed for 992 (27%), 906 (24%), and 441 (12%) patients, respectively (Table 1).

Study parameters

Effectiveness

The average LOS in the ED was 10.7 ± 41.1 hours for “chest radiography,” 5.61 ± 4.29 hours for “chest CT in the presence of respiratory symptoms,” 6.73 ± 4.08 hours for “systematic ULD chest CT,” and 8.19 ± 24.5) for “no systematic imaging” in the unadjusted population ($p < 0.001$).

Incremental costs and outcomes

The average 60-day unadjusted cost in euros was estimated at €3549 ± 7955), €3574 ± 7151, €4471 ± 7 822, and €2142 ± 4993, respectively, for “chest radiography,” “chest CT in the presence of respiratory symptoms,” “systematic ULD chest CT,” and “no systematic imaging” (Table 2).

Summary of main results

Inverse probability weighting using propensity scores led to a better standardized difference of means < 0.2 for the variables included in the logistic model (Fig. 2). The incremental LOS in the ED and the incremental cost in euros with inverse probability weighting are presented in Table 3. The least effective strategy was “no systematic imaging,” with an incremental of 10.8 (8.92; 13.1) hours in the ED. The ICER was €26 (saved) for a 1-hour reduction in the LOS in the ED using “systematic ULD chest CT” compared with “chest radiography” (cost difference = €98; efficacy difference = 3.8 hours) (Table 3).

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Table 1
Cohort characteristics, length of stay in the ED, and outcome

	Chest radiography (n = 906)	Chest CT if respiratory symptoms (n = 441)	Systematic ULD chest CT (n = 1373)	No systematic imaging (n = 992)	p
Age (y), mean ± SD	59.6 ± 20.1	59 ± 20.9	62.3 ± 18.9	52.9 ± 19.7	**<0.001**
Sex					
Male, n (%)	453 (50)	221 (50)	750 (55)	519 (52)	0,13
Female, n (%)	453 (50)	220 (50)	623 (45)	473 (48)	
Medical history					
Asthma, n (%)	116 (13)	53 (12)	143 (10)	108 (11)	0.32
COPD, n (%)	99 (11)	36 (8.2)	142 (10)	46 (4.6)	**<0.001**
Diabetes, n(%)	160 (18)	73 (17)	339 (25)	107 (11)	**<0.001**
High blood pressure, n (%)	327 (36)	157 (36)	621 (45)	220 (22)	**<0.001**
Immunosuppression, n (%)	71 (7.8)	16 (3.6)	64 (4.7)	61 (6.1)	**<0.001**
Clinical presentation					
Fever, mean ± SD (degrees)	37.3 ± 0.9	37.5 ± 1.1	37.2 ± 1.11	37.1 ± 0.815	**<0.001**
Oxygen saturation, mean ± SD (%)	95.8 ± 3.9	95.3 ± 3.9	95.2 ± 4.7	97.3 ± 3.6	**<0.001**
Heart rate, mean ± SD (per minute)	91.1 ± 18.9	90.3 ± 18.8	88.8 ± 18.5	92.4 ± 18.1	**<0.001**
Systolic blood pressure, mean ± SD (mmHg)	137 ± 23.0	137 ± 22.3	134 ± 24.1	133 ± 22.4	**<0.001**
Days with symptoms, mean ± SD	6.1 ± 5.4	5.9 ± 5.1	6.2 ± 4.6	5.6 ± 5.5	0.12
Cough, n (%)	581 (64)	261 (59)	966 (71)	521 (57)	**<0.001**
Shortness of breath, n (%)	595 (66)	237 (54)	989 (72)	434 (47)	**<0.001**
Chest pain, n (%)	271 (30)	70 (16)	322 (24)	143 (16)	**<0.001**
Diarrhea, n (%)	202 (22)	79 (18)	332 (24)	195 (21)	**0.03**
Aches and pain, n (%)	173 (19)	89 (20)	375 (27)	160 (21)	**<0.001**
Confusion, n (%)	52 (5.7)	15 (3)	120 (8.8)	33 (3.6)	**<0.001**
Results of imaging in the ED					
Compatible with COVID-19 lesions, n (%)	116 (14)	89 (33)	766 (56)	98 (17)	**<0.001**
Indeterminate, n (%)	143 (17)	9 (3.4)	116 (8.5)	8 (1.4)	
Other abnormalities, n (%)	120 (14)	3 (1.1)	186 (14)	5 (0.89)	
No abnormalities, n (%)	476 (56)	166 (62)	296 (22)	450 (80)	
Length of stay in the ED (hr), mean ± SD	10.7 ± 41.1	5.61 ± 4.3	6.73 ± 4.1	8.19 ± 24.5	**<0.001**
Care pathway after ED					
Discharge from the ED, n (%)	430 (47)	209 (47)	402 (29)	498 (50)	**<0.001**
Hospitalization in the short-stay unit, n (%)	165 (20)	12 (2.7)	552 (41)	24 (4.7)	**<0.001**
Hospitalization in intensive care unit, n (%)	83 (9.2)	25 (5.7)	198 (15)	50 (6.7)	**<0.001**
Length of hospitalization (days), mean ± SD	5.7 ± 6.3	7.5 ± 9.7	7.4 ± 10.4	5.2 ± 7.4	**<0.001**
RT-PCR positive in the ED, n (%)	224 (29)	67 (22)	808 (59)	270 (49)	**<0.001**
Diagnosis of COVID-19 in the ED, n (%)	259 (64)	103 (72)	966 (71)	324 (46)	<0.001
Death within 30 days, n (%)	40 (4.5)	98 (22)	102 (8.9)	53 (7.4)	<0.001

COPD, chronic obstructive pulmonary disease; ED, emergency department; ULD, ultra–low-dose.

Table 2
Average costs per patient in € in each imaging strategy group in the unadjusted population

Costs mean (SD)	Chest radiography (n = 906)	Chest CT if respiratory symptoms (n = 441)	Systematic ULD chest CT (n = 1373)	No systematic imaging (n = 992)
Consultation in the ED (in euros)	€22.1 ± 35.8	€25.8 ± 37.4	€1.9 ± 12.3	€44 ± 39.8
Imaging				
Radiography (in euros)	€5.9 ± 9.5	€0.5 ± 3.3	€0 ± 0	€0.5 ± 3.1
CT (in euros)	€0 ± 0	€1.3 ± 5.51	€0.6 ± 3.87	€1 ± 5
Hospitalization (in euros)	€2837 ± 5430	€3335 ± 7024	€3975 ± 7277	€1738 ± 3900
Rehospitalization (in euros)	€684 ± 5869	€211 ± 1344	€494 ± 2890	€360 ± 2829
Total cost (in euros)	€3549 ± 7955	€3574 ± 7151	€4471 ± 7822	€2142 ± 4993

Total cost rounded up to the nearest unit.
ED, emergency department; ULD, ultra–low-dose.

The efficiency frontier presented in Fig. 3 shows that the "chest radiography" strategy for triage was extendedly dominated.

Effect of uncertainty

The set of ICERs estimated using non-parametric bootstrapping is presented as a scatterplot on the cost-effectiveness plane, with "no systematic imaging" strategy (less costly) as the reference (Fig. 4). For "chest radiography," scatterplot replications were located in all four quadrants (40% in the upper right-hand quadrant, 30% in the upper left-hand, 15% in the bottom right-hand, and 15% in the bottom left-hand). For "chest CT in the presence of respiratory symptoms" and "systematic ULD chest CT," respectively, 90% and 75% of the replications were located in the upper right-hand quadrant, indicating better clinical outcomes and higher costs than "no systematic imaging" strategy.

The acceptability curve (Fig. 5) showed that 45% of the replications of ICERs for "systematic ULD chest CT" and "no systematic imaging" strategy fell below €200 per hour gained in the ED. Given a willingness to pay of €325 per hour gained in the ED, there is a 70% probability that "systematic ULD chest CT" was the most cost-effective strategy.

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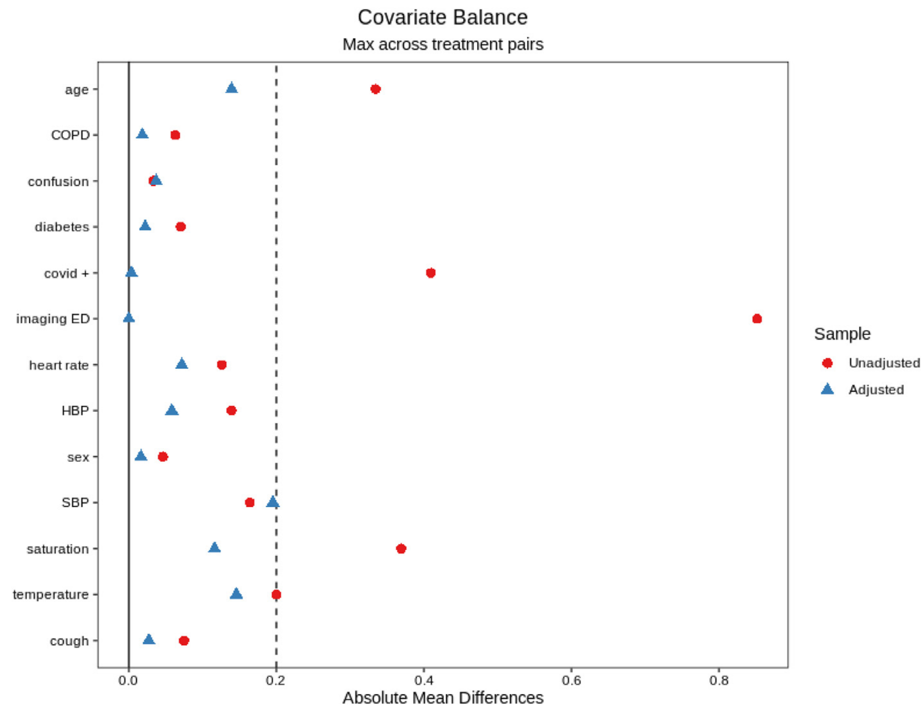

Fig. 2. Standardized mean difference in the unadjusted and adjusted with propensity score populations. COPD, chronic obstructive pulmonary disease; HBP, high blood pressure; SBP, systolic blood pressure; SMD, standardized mean difference.

Table 3
Deterministic sensitivity analysis

Determinant of sensitivity analysis	No systematic imaging	Cost of ULD chest CT	Efficacy of rapid RT-PCR and no systematic imaging	Efficacy of ULD chest CT	Cost difference	Efficacy difference	ICER(€/hour gained)
Base case	€2820	€3646	10.8	6.89	€826	3.91	211
Chest radiography (in euros)	€2840	€3648	10.8	6.89	€808	3.91	207
CT scan (in euros)	€2835	€3548	10.8	6.89	€713	3.91	182
ED visit (in euros)	€2941	€3653	10.8	6.89	€712	3.91	182
Hospitalization (in euros)	€13 947	€18 220	10.8	6.89	€4273	3.91	1092

We calculated the ICER as the average cost increment for the most cost-effective strategy, that is, systematic ULD chest CT, divided by the average effectiveness increment compared to the less costly strategy, that is, no systematic imaging.
CT, computed tomography; ED, emergency department; ICER, incremental cost-effectiveness ratio; ULD, ultra−low −dose.

Characterizing heterogeneity

In the deterministic sensitivity analysis, we calculated the ICER as the average increment of cost divided by the average increment of effectiveness for the more cost-effective strategy compared to the less costly strategy (“no systematic imaging”) to determine the robustness of our results. “Systematic ULD chest CT” remained cost-effective when substituting imaging and ED visit costs. When increasing the cost of hospitalization, the cost of “systematic ULD chest CT” was higher, with an ICER of €1092/hour gained in the ED (Table 4).

Discussion

The burden that the SARS-CoV-2 pandemic has placed on ED in hospitals highlights the need for an effective and efficient triage strategy. In this study of consecutive patients presenting in the ED with COVID-like symptoms, workup with “chest radiography” and “no systematic imaging” were the least effective strategies with regard to LOS. Compared to these, “systematic ULD chest CT” decreased the LOS in the ED by almost 4 hours at a cost increase of approximately €100 per patient compared with “chest radiography.” “Chest CT in the presence of respiratory symptoms” was more effective than “systematic ULD chest CT,” with the former providing a gain of 37 minutes at an extra cost of €718.

Given a willingness to pay of €325 per hour gained in the ED, there was a 70% probability that “systematic ULD chest CT” was the most cost-effective strategy.

Few studies have reported the effectiveness of diagnostic workup for patients with COVID-like symptoms in the ED during the first wave [13]. However, the management of patients in the ED during this period has consequences. A multicenter retrospective European cohort study revealed that there was a four-fold higher risk of death at the ED for acute cardiovascular admissions during the first wave [20]. In addition, it is crucial to consider the costs of diagnostic workup strategies performed in the ED. Thus, rapid antigen testing represents an alternative to RT-PCR for rapid diagnosis in the ED. Compared to clinical judgement alone, point-of-care rapid antigen testing in the ED in Germany reduced hospital expenditure to confirm or exclude COVID-19 [21]. Imaging is another way to improve

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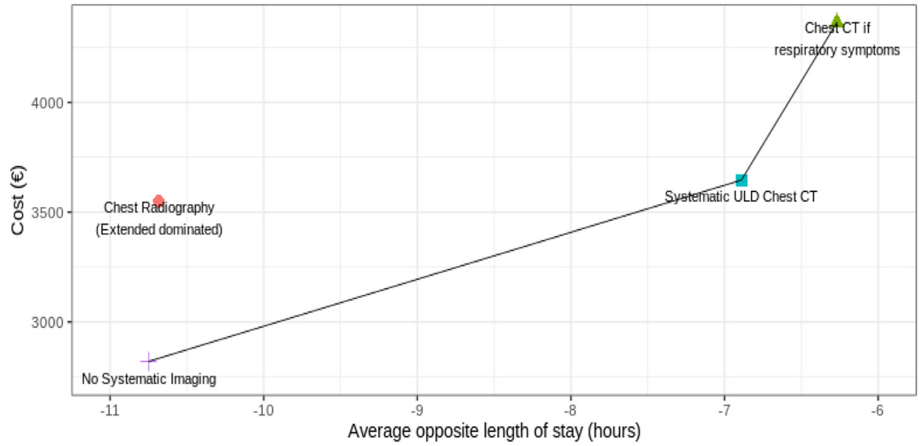

Fig. 3. Efficiency frontier of strategies “chest radiography” extended dominated, “chest CT if respiratory symptoms,” “systematic ultra-low-dose chest CT,“, and “no systematic imaging.” ED, emergency department; ULD, ultra–low-dose.

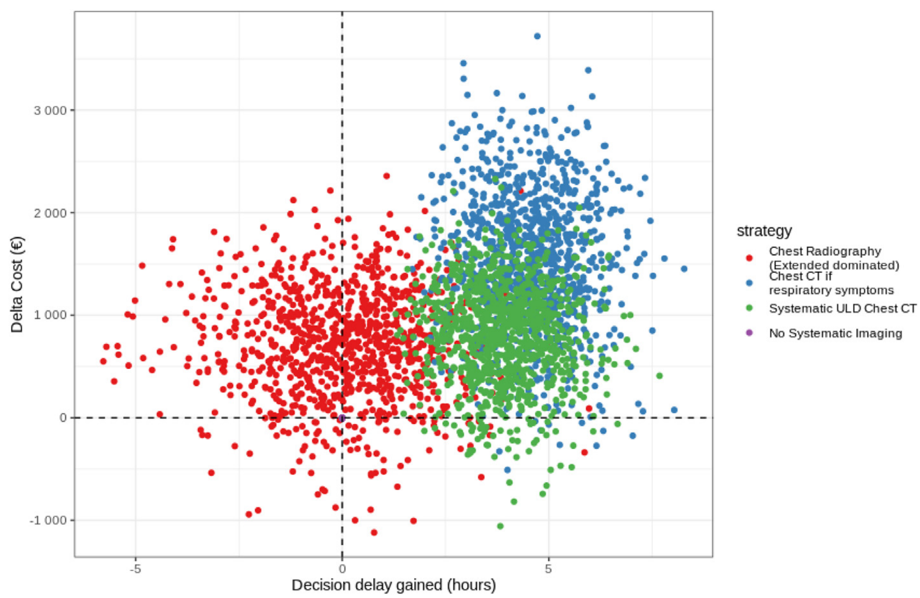

Fig. 4. Scatter plot of incremental cost and effectiveness of strategies “chest radiography,” “chest CT if respiratory symptoms,” and “systematic ultra–low-dose chest CT” compared to the strategy “no systematic imaging” (the less costly strategy). ED, emergency department; ULD, ultra–low-dose.

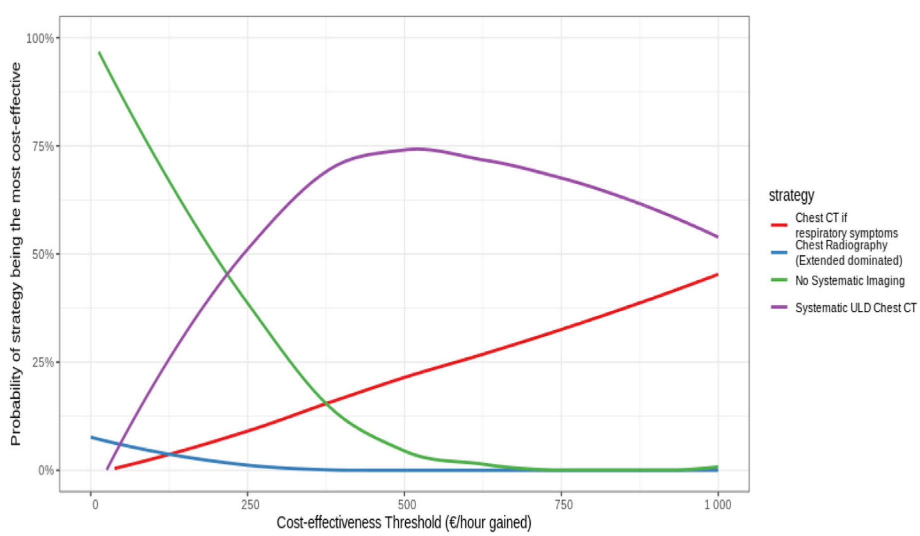

Fig. 5. Acceptability curve for strategies “chest radiography,” “chest CT if respiratory symptoms,” “systematic ultra–low-dose chest CT,” and “no systematic imaging.” ED, emergency department; ULD, ultra–low-dose.

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Table 4
Costs and effectiveness for each imaging strategy (weighted endpoints)

Strategy (95% CI)	No systematic imaging ($n = 992$)	Chest radiography ($n = 906$)	Systematic ULD chest CT ($n = 1373$)	Chest CT if respiratory symptoms ($n = 441$)
Effectiveness (hours in the ED)	10.8 (8.92–13.1)	10.7 (8.42–13.9)	6.89 (6.54–7.24)	6.27 (5.70–6.85)
Cost per patient (in euros)	€2820 (1959–3804)	€3548 (3072–4106)	€3646 (3310–4028)	€4364 (3554–5326)
Efficacy difference[a] (time in the ED)	NA	0.066 (-3.53–3.28)	3.79 (1.55–7.12)	0.622 (-0.0565–1.27)
Cost difference * (in euros)	NA	€728 (-349–1706)	€97.7 (-465–642)	€718 (-181–1738)
ICER = cost per hour gained in the ED (in euro per hour)	NA	11,030 (-5618–7300)	25.8 (-159–226)	1154 (-1326–8424)

ED, emergency department; ULD, ultra–low –dose.
[a] Difference was calculated using the immediately less costly strategy.

the diagnosis process in the ED, providing immediate results [22,23], especially during the first wave. In the actual context with the use of rapid and highly reliable testing, the conclusions of our study could be debated. However, in addition to a rapid diagnosis, the main effect of the imaging strategy concerned an efficient triage with organizational benefits by improving orientation after ED (discharge or transfer in a relevant medical ward) to optimize ED patient's flow. Indeed, at the time of our study without rapid testing available, earlier diagnosis with imaging alone helped to improve bed assignments and decisions on isolation in those that are highly suspected of having COVID-19. In the same way, a previous study revealed that a strategy combining antigen-detecting rapid diagnostic tests and chest CT was effective in ruling out COVID-19 and could reduce ED stays [24]. A strategy combining Ag testing and imaging could have been a more efficient strategy than imaging alone.

Limitations and strengths

The primary limitation of this study was its retrospective nature; factors other than the strategy applied for the diagnostic workup could explain the difference of LOS in the ED. However, we performed inverse probability weighting using propensity scores to consider the heterogeneity between the groups.

Furthermore, we took into account costs in the ED and subsequent hospital costs which resulted from the initial management.

Another limitation concerns the generalization of the findings given that costs differ by country. The average costs in the UK and in Germany is respectively among £101 and €150 for chest radiography as it is from £84 to £136 and €100 for chest CT [25–27]. To account for these differences between healthcare systems, we performed a deterministic sensitivity analysis. When we varied costs to reflect health costs in different countries, systematic ULD chest CT remained cost-effective across broad settings.

Finally, not many hospitals have the capacity to add an unlimited number of CTs, which could have collateral damage when other patients might suffer a delay in diagnosis and a longer stay in the ED.

To our knowledge, our study is the first cost-effectiveness study to evaluate the effect of imaging strategies in the clinical management of patients presenting with COVID-like symptoms [5]. LOS in the ED was chosen instead of diagnostic accuracy to evaluate the effect of imaging strategies on care pathways for patients admitted to the ED. At the time of the COVID pandemic when rapid triage was needed to optimize patient's flow, ED occupancy appeared the better performance criterion. The results of our study suggest that "systematic ULD chest CT" performed in the ED is the most cost-effective triage strategy to ensure that patients spend less time in the ED. These results provide important data for recommendations related to the diagnostic workup of patients with COVID-like symptoms in the ED. Furthermore, our deterministic sensitivity analysis varied costs to reflect health costs in different countries and showed that "systematic ULD chest CT" in the ED remained cost-effective. However, when the cost of hospitalization was increased to five times, the cost of "systematic ULD chest CT" was high, with an ICER of €1092/hour gained in the ED. ICER was the most sensitive to the cost of hospitalization. Patient profiles could explain this. Indeed, regarding this strategy, a larger proportion of patients were subsequently hospitalized (97.5% vs. 45.1%), more frequently had a COVID-19 diagnosis because of a higher prevalence of COVID-19 in the center, and more patients were hospitalized in the intensive care unit (71% vs. 46% and 15% vs. 6.7%, respectively).

Conclusion

In this large cohort study, "systematic ULD chest CT" for patients with COVID-like symptoms is a cost-effective strategy that reduces the LOS in EDs to 4 hours per patient, with an increased average cost of €98 per patient compared to "chest radiography" and €826 compared to "no systematic imaging." Our results support the utilization of this strategy during the pandemic with the need of triage patients in the ED improving the management of patients in the absence of point-of-care detection. This potentially cost-effective strategy can optimize the consumption of healthcare system resources.

Transparency declaration

The authors declare that they do not have any competing interests concerning this study.

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Author contributions

SK, MO, IZD, and PB conceived the study and designed the trial. SK, MO, IZD, and PB supervised the trial and data collection. SK, DV, NM, OT, OP, VW, JM, EV, TD, TM, SH, PLB, EB, NL, YH, and SFK recruited the participating centers and patients, and managed the data, including quality control. SK, KZ, and IDZ provided statistical advice about the study design and analyzed the data. SK drafted the manuscript, and all authors contributed substantially to its revision. SK takes responsibility for the paper as a whole.

This study was conducted in accordance with the principles set forth by the Good Clinical Practice guidelines and the Declaration of Helsinki. The study was approved by the ethics committee (CE 2021-141). This study was registered with the Clinical Trials Registry (NCT05077228).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.05.036.

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