Tomosynthesis for the detection of pulmonary emphysema: Diagnostic performance as compared to chest radiography, using multidetector-row computed tomography as reference

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Purpose

Emphysema is defined as a "condition of the lung characterized by abnormal, permanent enlargement of the air spaces distal to the terminal bronchiole, accompanied by destruction of alveolar walls" [1]. Pulmonary emphysema is a major contributor to chronic obstructive pulmonary disease and remains one of the leading causes of morbidity and mortality worldwide. Despite encouraging smoking cessation efforts in some parts of the world, this disease is expected to remain an important health care problem in the world for decades to come [2].

There has been a longstanding interest in thoracic imaging for in vivo characterization of emphysema. Research in this area has spanned readily available modalities such as chest radiography and computed tomography (CT). Chest radiography remains the most commonly used technique for the diagnosis and follow-up of pulmonary diseases; its advantages are the short examination time, easy accessibility, and low cost [3, 4]. However, chest radiography lacks sensitivity for the detection of mild emphysema [5]. More recently, CT has become the standard modality for objective evaluation of lung diseases [6], and considerable research effort has been devoted to the quantification of emphysema by CT [2, 7]. However, CT remains relatively expensive and involves considerable radiation exposure of the patients [8, 9].

Digital tomosynthesis is a type of limited-angle tomography that allows reconstruction of multiple image planes from a set of projection data acquired over a finite range of movements of the x-ray tube [10-12]. Its advantages are that it removes visual interference from overlying structures, provides depth information on structures, and involves lower radiation exposure of the patients than CT [13-17]. Furthermore, the cost of tomosynthesis is lower than that of CT [16, 18, 19]. Previous reports have indicated the superior detection sensitivity of digital tomosynthesis to that of chest radiography for CT-proven pulmonary nodules [15, 16, 20]. However, to the best of our knowledge, no clinical study until date has evaluated the diagnostic performance of tomosynthesis for the detection of pulmonary emphysema.

The purpose of this study was to compare the diagnostic performance of tomosynthesis with that of chest radiography for the detection of pulmonary emphysema, using multidetector-row computed tomography (MDCT) as reference.

Methods and Materials

Patients
Our institutional review board approved the conduct of this study. We performed a retrospective review of tomosynthesis scans in 406 consecutive patients with suspected pulmonary nodules who underwent radiography, tomosynthesis and MDCT on the same day for the study purpose at our hospital between May 2010 and April 2011. All patients provided written informed consent, including for use of the images and medical records for research purposes. The inclusion criteria for patients in this study were: older than 18 years old and not pregnant. Of the 406 patients, 48 patients were diagnosed as having pulmonary emphysema by MDCT, and served as the study group (male/female: 44/4, age: 69.7 ± 9.8 years); then, a total of 63 patients diagnosed as not having emphysema were randomly selected and enrolled as the control group (male/female: 43/20, age: 62.6 ± 12.8 years). The height and weight of the patients were measured, and the body mass index was calculated as the weight in kilograms divided by height squared in meters.

**Imaging protocol**

Chest radiography (RADspeed, Shimadzu, Nakagyo-ku, Kyoto, Japan) included upright posteroanterior and lateral views obtained at a tube voltage of 130 kVp, with automatic control of the patient exposure. The effective dose for a standard patient in this study (height, 161 cm; weight, 61 kg) was approximately 0.03 mSv for the posteroanterior view and 0.11 mSv for the lateral view, determined using an anthropomorphic chest phantom (Lung/Chest Phantom LSCT-001, Kyoto Kagaku, Fushimi, Kyoto, Japan), PC-based x-ray Monte Carlo program (PCXMC 2.0) (Radiation and Nuclear Safety Agency, Helsinki, Finland) [21], and International Commission on Radiological Protection (ICRP) publication 103 [22].

For tomosynthesis, the SONIALVISION safire radiography/fluoroscopy system (Shimadzu, Nakagyo-ku, Kyoto, Japan) equipped with a direct-conversion digital flat panel detector under the radiographic tilt table was used. The table was tilted to an angle of 80 degrees to reduce physiological motion artifacts [20]. The direct-conversion digital flat panel detector was used in the 15 frames-per-second mode and 38-cm to 43-cm x 38-cm to 43-cm field of view, depending on the patient's body habitus. The scan range was fixed and the scan depth was adjusted to the patient characteristics up to 30 cm in the anteroposterior direction. Under these settings, the acquisition time for 74 frames over the tube movement range of +/- 20 degrees was 5 seconds. The acquisition parameters were 120 kVp, 25 mA and 1.6 ms. The effective dose for a standard patient was approximately 0.19 mSv, determined as previously mentioned. The examination yielded approximately 41 reconstructed coronal images with a thickness of 5 mm. The tomosynthesis images covered the entire chest in all patients.

MDCT of the chest was performed with a 16-row multidetector scanner (BrightSpeed, GE Healthcare, Waukesha, Wisconsin, USA). The technical parameters were as follows: rotation time, 500 ms; beam collimation, 16 x 0.625 mm; normalized pitch, 1.75; z-axis coverage, 20 mm; tube voltage, 120 kV; tube current, 100 to 180 mA, depending
on the patient size; field of view, 50 cm. Image reconstruction was performed in a 25-cm to 40-cm display field of view, depending on the patient’s body habitus. The axial images were reconstructed into 1.25-mm-thick images without overlap. The computed-tomographic effective dose estimate was 2 to 3 mSv, determined by dose-length product measurements and appropriate normalized coefficients indicated in the European guidelines for chest CT [0.017 mSv/(mGy • cm)] [23].

Detection Study

Two board-certified radiologists with 10 years’ and 7 years’ experience, and a 1-year clinical experience each in chest tomosynthesis, independently evaluated the tomosynthesis images and radiographs for the presence of pulmonary emphysema. The images were evaluated using a software (ShadeQuest/DIAG, Yokogawa, Musashino-shi, Tokyo, Japan) designed for displaying medical images. On both the tomosynthesis images and radiographs, the diagnosis of emphysema was based on previously proposed criteria [5, 24, 25], as follows:

1. Increased radiolucency of the lung fields
2. Flattening of the diaphragms
3. Pruning of the peripheral vasculature
4. Increased retrosternal airspace (on lateral-view radiographs)
5. Widening of the intercostal spaces
6. Narrowed and more vertical cardiac silhouette

The readers were provided with no clinical information, including in respect of the ratio of the emphysema to non-emphysema cases. They were allowed to change the window width and window level and to use the pan/zoom functions and gray-scale inversion at the workstation. They were asked to grade their degree of confidence in regard to the diagnosis of emphysema on a scale of 1 to 4, with the rating of 4 representing the highest degree of confidence (definitely emphysema) and that of 1 representing the lowest degree of confidence (possible emphysema). The readers were also advised to ignore the pulmonary nodules, parenchymal scars, interstitial changes, and extrapulmonary lesions, such as bone islands, rib fractures, and cardiac calcification. To eliminate systematic bias in the reading of the images, the order of reading the images from the two modalities were randomly classified into two sessions, particular to each reader. Each case occurred only once in each session (i.e., if the tomosynthesis image was included in the first session, the radiograph was included in the second session). The interval between the 2 reading sessions was 3 weeks.

Reference Method
MDCT images served as the reference for the diagnosis of pulmonary emphysema. The reference was created by the consensus of two board-certified radiologists with 10 years' and 27 years' experience, who did not participate in the detection study. In addition, quantitative measurement of the emphysema was performed using Airway Inspector (a free, open-source tool used for CT-based image analysis available at www.airwayinspector.org), which was also used to evaluate pulmonary emphysema in the previous study [26]. The percentage of the lung volume that was emphysematous was calculated based on a threshold of -950 Hounsfield units (relatively low-attenuation area with attenuation values of -950 HU or lower [LAA$_{-950}$]), as described in previous studies [27, 28].

Pulmonary emphysema as reference standard was diagnosed by both (1) detection of qualitative emphysematous changes on the axial and coronal MDCT images by experienced radiologists and (2) determination of an LAA$_{-950}$ value of more than 3% on the axial MDCT images.

The diagnoses made on the tomosynthesis images and radiographs by the readers were compared with the diagnosis made on the MDCT images used as the reference standard. The possible causes of the false-negative, true-positive and false-positive diagnoses were evaluated retrospectively.

**Statistical Analysis**

Receiver-operating characteristic (ROC) analysis was used to compare the diagnostic performance of tomosynthesis with that of radiography; MDCT served as the reference standard to establish the presence/absence of emphysema. The area under the curve (AUC) and its 95% confidence interval (CI) were calculated for each of the techniques and readers. The sensitivity, specificity, positive predictive value and negative predictive value of tomosynthesis and radiography were estimated by treating a rating of greater than 1 as a positive test result. Interobserver agreement was evaluated by measuring the Kappa statistic between the two radiologists for the diagnosis of emphysema. To investigate the effect of the LAA$_{-950}$ value on the diagnostic sensitivity, generalised estimating equations (GEE) containing reader and LAA$_{-950}$ (cut-off value, median) as factors was fitted by techniques. GEE model containing LAA$_{-950}$ as a covariate, and reader and technique as factors, was also fitted. In these two GEE analyses, a rating of greater than 1 was treated as a positive test result. The working correlation matrix was compound symmetry, and the link function was the logit in both models. The significance level for all tests was two-sided, at 5%. All data were analysed using a commercially available software program (SAS version 9.1, SAS, Cary, NC, USA) and the graphs were generated within the software program (Microsoft Excel 2007, Microsoft, Redmond, WA, USA).
Results

Patient characteristics

The mean height, weight and body mass index of the 48 patients diagnosed as having emphysema were 163.3 ± 6.2 cm (range, 149.0-178.0 cm), 60.5 ± 8.1 kg (range, 42.0-79.0 kg) and 22.6 ± 2.4 kg/m² (range, 17.3-28.7 kg/m²), respectively. The mean height, weight and body mass index of the 63 patients who did not have emphysema were 161.4 ± 7.1 cm (range, 149.0-176.0 cm), 61.6 ± 12.5 kg (range, 41.0-92.0 kg) and 23.5 ± 3.4 kg/m² (range, 18.0-30.9 kg/m²), respectively. The mean LAA₉₅₀ in the patients with emphysema was 12.1 ± 7.7% (range, 3.0-39.9%).

Overall diagnostic performance

The ROC curves for each modality and reader are shown in Fig. 1 on page 9. Nonparametric AUC values for the modalities and readers are summarized in Table 1.

<table>
<thead>
<tr>
<th>Area under the curve in ROC (95% CI)</th>
<th>Reader 1</th>
<th>Reader 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tomosynthesis</td>
<td>0.937 (0.889, 0.985)</td>
<td>0.911 (0.863, 0.960)</td>
</tr>
<tr>
<td>Radiography</td>
<td>0.698 (0.615, 0.781)</td>
<td>0.703 (0.620, 0.786)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 1: Area under the curve in ROC for each modality and reader

ROC: receiver-operating characteristic

CI: confidence interval

For both readers, the AUC for tomosynthesis (reader 1, 0.937 [95% CI: 0.899, 0.985]; reader 2, 0.911 [95% CI: 0.863, 0.960]) was significantly higher than that for radiography (reader 1, 0.698 [95% CI: 0.615, 0.781]; reader 2, 0.703 [95% CI: 0.620, 0.786]). The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) are summarized by modality and reader in Table 2.
<table>
<thead>
<tr>
<th>Modality</th>
<th>Reader</th>
<th>Sensitivity</th>
<th>(95% CI)</th>
<th>Specificity</th>
<th>(95% CI)</th>
<th>PPV</th>
<th>(95% CI)</th>
<th>NPV</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tomosynthesis</td>
<td>1</td>
<td>0.896</td>
<td>(0.773, 0.965)</td>
<td>0.984</td>
<td>(0.915, 1.000)</td>
<td>0.977</td>
<td>(0.880, 0.999)</td>
<td>0.925</td>
<td>(0.834, 0.975)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.854</td>
<td>(0.722, 0.939)</td>
<td>0.952</td>
<td>(0.867, 0.990)</td>
<td>0.932</td>
<td>(0.813, 0.986)</td>
<td>0.896</td>
<td>(0.797, 0.957)</td>
</tr>
<tr>
<td></td>
<td>Average</td>
<td>0.875</td>
<td>(0.722, 0.939)</td>
<td>0.968</td>
<td>(0.867, 0.990)</td>
<td>0.955</td>
<td>(0.813, 0.986)</td>
<td>0.910</td>
<td>(0.797, 0.957)</td>
</tr>
<tr>
<td>Radiography</td>
<td>1</td>
<td>0.500</td>
<td>(0.352, 0.648)</td>
<td>0.873</td>
<td>(0.765, 0.944)</td>
<td>0.750</td>
<td>(0.566, 0.885)</td>
<td>0.696</td>
<td>(0.582, 0.795)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.458</td>
<td>(0.314, 0.608)</td>
<td>0.952</td>
<td>(0.867, 0.990)</td>
<td>0.880</td>
<td>(0.688, 0.975)</td>
<td>0.698</td>
<td>(0.589, 0.792)</td>
</tr>
<tr>
<td></td>
<td>Average</td>
<td>0.479</td>
<td>(0.314, 0.608)</td>
<td>0.913</td>
<td>(0.867, 0.990)</td>
<td>0.815</td>
<td>(0.688, 0.975)</td>
<td>0.697</td>
<td>(0.589, 0.792)</td>
</tr>
</tbody>
</table>

**Table 2: Sensitivity, Specificity, PPV and NPV by modality and reader**

CI: confidence interval

PPV: positive predictive value

NPV: negative predictive value

For tomosynthesis, the average sensitivity, specificity, PPV, and NPV were 0.875, 0.968, 0.955, and 0.910, respectively, whereas, for radiography, the corresponding values were 0.479, 0.913, 0.815, and 0.697, respectively.

In Fig. 2-8, an example of pulmonary emphysema correctly diagnosed on tomosynthesis images (Fig. 2 on page 10 and Fig. 3 on page 11), but not on radiographs (Fig. 4 on page 12, Fig. 5 on page 13 and Fig. 6 on page 14), is shown along with the
corresponding MDCT images (Fig. 7 on page 15 and Fig. 8 on page 16). Note that the emphysematous spaces (arrows) are much easier to recognize on the tomosynthesis images (Fig. 2 on page 10 and Fig. 3 on page 11) than on the radiographs (Fig. 4 on page 12, Fig. 5 on page 13 and Fig. 6 on page 14). The positions and shapes of the diaphragms seem to be normal and the cardiac silhouette is not narrowed on the radiographs (Fig. 4 on page 12 and Fig. 5 on page 13).

The Kappa statistic, calculated to express the interobserver agreement between the two radiologists, was 0.925 (95% CI: 0.852, 0.997) for tomosynthesis and 0.695 (95% CI: 0.542, 0.847) for radiography.

Association of the diagnostic sensitivity with the LAA.950 values

The median LAA.950 in the patients with emphysema in this study was 10.65%. The average diagnostic sensitivity of tomosynthesis in patients with LAA.950 values ≥ 10.65% was significantly higher as compared with that in patients with LAA.950 values < 10.65% (P = 0.005; 0.979 vs. 0.771). A similar trend was observed for the diagnostic sensitivity of radiography (P = 0.025; 0.667 vs. 0.291) (Table 3).

<table>
<thead>
<tr>
<th>Modality</th>
<th>Reader</th>
<th>LAA.950&lt;10.65%</th>
<th>LAA.950≥10.65%</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tomosynthesis</td>
<td>1</td>
<td>0.792 (19/24)</td>
<td>1.000 (24/24)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.750 (18/24)</td>
<td>0.958 (23/24)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Average</td>
<td>0.771</td>
<td>0.979</td>
<td>0.005</td>
</tr>
<tr>
<td>Radiography</td>
<td>1</td>
<td>0.375 (9/24)</td>
<td>0.625 (15/24)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.208 (5/24)</td>
<td>0.708 (17/24)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Average</td>
<td>0.291</td>
<td>0.667</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Table 3: Subgroup analysis of the diagnostic sensitivity by the LAA.950 (cutoff: median value)

Note-Data represent the sensitivity.

10.65% was the median of LAA.950 measured on multidetector-row computed tomography images.
*: Average results for the readers were tested using generalized estimating equations (GEE).

LAA\textsubscript{-950}: relatively low-attenuation area with attenuation values of -950 HU or lower

A similar association between the sensitivity and LAA\textsubscript{-950} was observed when LAA\textsubscript{-950} was treated as a continuous variable in the GEE analysis (P = 0.0005) (Table 4).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>SE</th>
<th>Z</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.1417</td>
<td>0.6251</td>
<td>0.23</td>
<td>0.8207</td>
</tr>
<tr>
<td>Reader</td>
<td>0.2796</td>
<td>0.2115</td>
<td>1.32</td>
<td>0.1862</td>
</tr>
<tr>
<td>Modality</td>
<td>-2.3566</td>
<td>0.4357</td>
<td>-5.41</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LAA\textsubscript{-950}</td>
<td>0.1482</td>
<td>0.0426</td>
<td>3.48</td>
<td>0.0005</td>
</tr>
</tbody>
</table>

Table 4: Parameter estimates and their standard errors with generalized estimating equations (GEE)

SE: standard error

LAA\textsubscript{-950}: relatively low-attenuation area with attenuation values of -950 HU or lower

These results suggest the robustness of this association between the diagnostic sensitivity and the LAA\textsubscript{-950}.

Images for this section:
**Fig. 1:** Receiver-operating characteristic curves for tomosynthesis and chest radiography for the two readers participating in the detection study.
**Fig. 2:** A 59-year-old man with pulmonary emphysema who had an LAA-950 value of 10%: tomosynthesis image.
Fig. 3: A 59-year-old man with pulmonary emphysema who had an LAA-950 value of 10%: tomosynthesis close-up image.
Fig. 4: A 59-year-old man with pulmonary emphysema who had an LAA-950 value of 10%: posteroanterior radiograph.
**Fig. 5:** A 59-year-old man with pulmonary emphysema who had an LAA-950 value of 10%: lateral radiograph.
Fig. 6: A 59-year-old man with pulmonary emphysema who had an LAA-950 value of 10%: posteroanterior radiograph close-up image.
Fig. 7: A 59-year-old man with pulmonary emphysema who had an LAA-950 value of 10%: multidetector-row computed tomography (MDCT) coronal image (reference standard).
**Fig. 8:** A 59-year-old man with pulmonary emphysema who had an LAA-950 value of 10%: MDCT close-up image.
Conclusion

Numerous methods have been proposed to address the perceptual limitations of chest radiography, with varying degrees of success [11]. Digital tomosynthesis has been shown to offer substantial improvement over conventional chest radiography for the detection of subtle lung diseases [15, 16, 18, 19, 29]. In this study, ROC analysis showed significantly better performance of tomosynthesis than of chest radiography for the detection of pulmonary emphysema. To the best of our knowledge, this is the first study to evaluate the diagnostic performance of tomosynthesis for the detection of pulmonary emphysema.

Although chest radiography is the most commonly performed radiologic examination around the world, a low sensitivity and low specificity are major limitations of this diagnostic tool. The problems related to the limited sensitivity and specificity of radiography have been resolved to a large extent with the introduction of CT. However, with the increasing use of CT, the high radiation exposures of the patients and high costs have become problematic. With regard to the radiation dose, increased use of CT around the world has also raised concern about the increased risk of cancer from medical radiation exposure [30]. Since radiation-induced carcinogenesis is a stochastic effect, the risk may be expected to decrease with a decrease of the radiation dose. In this study, the radiation exposure of the patient during tomosynthesis was less than one-tenth of that during chest MDCT and comparable to that during posteroanterior plus lateral chest radiography. From the cost perspective, the costs of MDCT, tomosynthesis, and posteroanterior plus lateral chest radiographic examinations, including their interpretations, are approximately $184-206, $53, and $36, respectively, in our country. Therefore, the cost of tomosynthesis is only about one-third to one-fourth as compared with that of MDCT. Thus, our results suggest that tomosynthesis provides a high diagnostic accuracy for the presence of pulmonary emphysema, at a much lower radiation exposure and cost to the patient as compared to MDCT, although tomosynthesis does not generally lend itself satisfactorily to objective analysis.

Also, our results showed significantly better performance of tomosynthesis than that of chest radiography for the detection of pulmonary emphysema. One explanation is that tomosynthesis substantially reduced the visual clutter of overlying anatomy in detecting the emphysematous change as compared to radiography. With regard to the interobserver agreement, clear separation between the 95% CIs of the Kappa statistics for tomosynthesis and radiography indicates that the interobserver agreement for tomosynthesis was significantly higher than that for radiography. Considering our results, tomosynthesis could be used as an alternative screening tool to chest radiography for pulmonary emphysema as well as pulmonary nodules, especially from the point of view of the almost comparable radiation dose and cost as compared to those for chest radiography. Meanwhile, in respect of the time taken for interpretation, the previous study reported that the mean interpretation time for whole pulmonary lesions in tomsynthesis (mean ± SD, 200 ± 40 s) was longer than that for radiography (120 ± 30 s), but
shorter than that for CT (600 ± 150 s) [31]. In our study, we focused on the diagnostic performance of tomosynthesis for the detection of pulmonary emphysema and evaluated only emphysema; therefore, we did not show the time of interpretation for only pulmonary emphysema, because, in the clinical setting, we usually evaluate all pulmonary lesions other than emphysema as well.

In this study, the average diagnostic sensitivity of radiography for emphysema in patients with \( LAA_{950} < 10.65\% \) was only 0.291, whereas that in patients with \( LAA_{950} \geq 10.65\% \) was 0.667. These results were consistent with previous reports stating that mild emphysema is rarely detectable by radiography [5, 32]. We found that the sensitivity of tomosynthesis also increased with increasing \( LAA_{950} \). This result is conceivable, especially when considering the results for radiography.

Although pulmonary function tests are reproducible both in the short- and the long-term, and have been used as the mainstay in the evaluation of patients with respiratory disorders, they are of limited value in the measurement of airway obstruction, particularly of the small airways, which are predominantly affected in emphysema [33], and autopsy studies have shown that up to one-third of the lung can be destroyed by emphysema before respiratory function parameters become impaired [2, 34]. Sanders et al. reported that features of emphysema could be visually detected on CT scans in 69% of smokers with normal test results for diffusing capacity of the lungs for carbon monoxide (DLCO), with or without evidence of obstructive deficit, and they concluded that CT may be more sensitive than pulmonary function tests in detecting mild emphysema [35]. Our results obtained using MDCT as reference indicate that tomosynthesis has a high diagnostic accuracy for the presence of emphysema. Earlier detection of emphysema by tomosynthesis than by radiography could lead to earlier recommendation of pulmonary function testing, earlier encouragement of smoking cessation, and/or earlier appropriate non-pharmacological/pharmacological therapy for chronic obstructive pulmonary disease, which could have a beneficial effect in regard to the rate of progression of the disease [36, 37].

Our study had several limitations. First, the size of the patient group was relatively small and further studies on larger numbers of patients must be performed. Second, recently, ultra-low dose CT has been acquired with less than 1mSv [38]. Further study to compare tomosynthesis with ultra-low dose CT at less than 1 mSv would be desirable; however, the cost of tomosynthesis will still be much lower than that of ultra-low dose CT.

In conclusion, the diagnostic performance of tomosynthesis was significantly superior to that of radiography for the detection of pulmonary emphysema. In both tomosynthesis and radiography, the sensitivity was affected by the \( LAA_{950} \).
References


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