Fully-Automated Liver Tumor Localization and Characterization from Multi-Phase MR Volumes Using Key-Slice ROI Parsing: A Physician-Inspired Approach

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Abstract. Using radiological scans to identify liver tumors is crucial for proper patient treatment. This is highly challenging, as top radiologists only achieve F1 scores of roughly 80% (hepatocellular carcinoma (HCC) vs. others) with only moderate inter-rater agreement, even when using multi-phase magnetic resonance (MR) imagery. Thus, there is great impetus for computer-aided diagnosis (CAD) solutions. A critical challenge is to reliably parse a 3D MR volume to localize diagnosable regions of interest (ROI). In this paper, we break down this problem using a key-slice parser (KSP\textsuperscript{3}), which emulates physician workflows by first identifying key slices and then localize their corresponding key ROIs. Because performance demands are so extreme, (not to miss any key ROI), our KSP integrates complementary modules—top-down classification-plus-detection (CPD) and bottom-up localization-by-over-segmentation (LBOS). The CPD uses a curve-parsing and detection confidence to reweight classifier confidences. The LBOS uses over-segmentation to flag CPD failure cases and provides its own ROIs. For scalability, LBOS is only weakly trained on pseudo-masks using a new distance-aware Tversky loss. We evaluate our approach on the largest multi-phase MR liver lesion test dataset to date (430 biopsy-confirmed patients). Experiments demonstrate that our KSP can localize diagnosable ROIs with high reliability (85% patients have an average overlap of $\geq 40\%$ with the ground truth). Moreover, we achieve an HCC vs. others F1 score of 0.804, providing a fully-automated CAD solution comparable with top human physicians.

Keywords: Liver · Tumor localization · Tumor characterization

\textsuperscript{*} B. Lai, X. Bai and Y. Wu — Equal contribution.
This work was done when X. Bai was intern at Ping An Technology.
1 Introduction

Liver cancer is the fifth/eighth most common malignancy in men/women worldwide [4]. During treatment planning, non-invasive diagnostic imaging is preferred, as invasive procedures, i.e. biopsies or surgeries, can lead to hemorrhages, infections, and even death [12]. Multi-phase magnetic resonance (MR) imagery is often considered the most informative radiological option [18], with T2-weighted imaging (T2WI) helping to reveal tumor edges and aggressiveness [2]. Manual lesion differentiation is workload-heavy, requiring radiologists with high expertise that may not be available in every medical center. Additionally, studies on human reader performance typically on differentiating hepatocellular carcinoma (HCC) from other types, report low specificities [2] and moderate inter-rater agreement [10]. Thus, there is a need for computer-aided diagnosis (CAD) solutions, which is the topic of our work. Unlike other approaches, we propose a physician-inspired workflow to achieve greater reliability and robustness.

A major motivation for CAD is addressing challenging cases that would otherwise be biopsied or even incorrectly operated on. For instance, a 2006 retrospective study discovered that pre-operative imaging misinterpreted 20% of its liver transplant patients as having HCC [11]. While several CAD approaches have been reported, many do not focus on histopathologically-confirmed studies [27,1,8,23], which are the cases most requiring CAD intervention. Prior CAD studies, except for Zhen et al. [30], also only focus on computed tomography (CT), despite the greater promise of MR. Most importantly, apart from two studies [7,16], CAD works typically assume a manually drawn region of interest (ROI) is available. In doing so, they elide the major challenge of parsing a medical volume to determine diagnosable ROIs. Without this capability, manual intervention remains necessary and the system also remains susceptible to inter-user variations. The most obvious localization strategy follows computer vision practices and directly applies a detector, e.g., [16]. However, detectors aim to find all lesions and their entire 3D extent in a study, whereas the needs for liver lesion characterization are distinct: reliably localize the key diagnosable ROI(s). This different goal warrants its own study, which we investigate.

In this work, we develop a robust and fully-automated CAD system to differentiate malignant liver tumors into the HCC, ICC and metastasis subtypes. Fig. 1(a) depicts these three types. To localize key diagnosable ROIs, we use a physician-inspired approach that departs from standard detection frameworks seen in computer vision and used elsewhere [16]. Instead, we propose a key-slice parser (KSP), which breaks down the parsing problem similarly to clinical practice, e.g., the ubiquitous response evaluation criteria in solid tumors (RECIST) protocol [9]. Key slices are first identified in the volume and, from each of these, a diagnosable ROI is regressed. Because reliability is so critical, our KSP integrates two complementary and reinforcing streams. The first is a top-down classification-plus-detection (CPD) workflow that combines together multi-sequence classification, detection, and curve parsing. The CPD can achieve high precision, but can fail to localize challenging edge cases, especially small tumors. Thus, we use a second bottom-up workflow that uses a localization-by-
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Fig. 1. (a) HCC, ICC and metastasis lesion examples on T2WIs, including large, medium, small and low contrast tumors. The “small” metastasis shows an example of a lesion cluster. (b) Different MR sequences of the same patient.

over-segmentation (LBOS) module, combined with a novel high-recall loss. For scalability, the LBOS is only weakly-trained on pseudo masks. The CPD and LBOS results are then merged together to produce a final set of ROIs. Each ROI is then classified using a standard classification network.

We test our approach on 430 multi-phase MR studies (2150 scans), which is the largest test cohort studied for liver lesion CAD to date. Moreover, all of our patient studies are histopathologically confirmed, well-representing the challenging cases requiring CAD. Using our KSP framework, we achieve very high reliability, with 85% of our predicted ROIs overlapping with the ground truth by $\geq 40\%$, outperforming the best detector alternative (only 79% with an overlap $\geq 40\%$). When connected with our characterization, our system can achieve an F1 score of HCC vs. others of 0.804, which is comparable to reported human physician performances of 0.791 [2].

2 Methods

Fig. 2 illustrates our approach, which comprises two main components: a key-slice parser (KSP) and a liver lesion classifier. KSP, in turn, is composed of two streams: (1) top-down classification-plus-detection (CPD), which enjoys high precision, and (2) bottom-up localization-by-over-segmentation (LBOS), which filters out unreliable CPD predictions and catches small ROIs missed by the CPD. Both KSP modules follow principles codified in clinical practice [9] of first finding a reliable key slice and then regressing one key ROI per slice.

As illustrated in Fig.1(b), we assume we are given a dataset of MR volumes with five sequences/ phases: unenhanced T1-weighted imaging (T1WI), arterial-phase T1-weighted imaging (T1WI-A), venous-phase T1-weighted imaging (T1WI-V), T2WI, and diffusion-weighted imaging (DWI). Formally, assuming N studies, we define our dataset as $D = \{X_i, B_i, y_i\}_{i=1}^N$, where $X_i = \{X_{i,j}\}_{j=1}^5$ is the set of five MR sequences and $y_i$ is the corresponding study-level lesion-type label. Lesions are either (1) annotated by 2D bounding boxes
(bboxes) using RECIST-style marks \[9\] or (2) when they are too numerous to be individually annotated, a bbox over each cluster is provided. See Fig. 1(a) for an illustration of the two types. Each study volume can be indexed by its slice \(m\), i.e., \(X_{i,j,m}\), which will also select the subset of bboxes defined on that slice, \(B_{i,m}\). From the bboxes, we can also define slices as being “key”, “marginal”, and “non-key”. Marginal slices are slices within a buffer of one slice from the beginning or end of any lesion. We will drop the \(i\) when appropriate.

For localization, we follow a consistent philosophy to handle the MR data. We note that the sequences or phases where lesions are visible vary considerably from lesion to lesion. Moreover, successful localization only requires detecting the lesion on one sequence. Using early fusion (EF) for localization, i.e., inputting a five-channel slice, can result in overfitting because the network may needlessly fit to the specific combinations of visible sequences found in training. Examining each MR sequence more independently avoids this pitfall. Thus, for all modules

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Fig. 2. The proposed (a) KSP framework composed of (b) CPD and (c) LBOS.
in KSP, we perform late fusion (LF). More specifically, because T2WI is the most informative sequence for liver tumors [2], we use T2WI as an anchor (T2-anchor) and pair each of the remaining sequences with it. We train separate models for each of the five MR sequences and then merge the results.

2.1 Classification-Plus-Detection

A KSP module operates by identifying key slices and regressing a key ROI from each slice. As Fig. 2 (b) illustrates, our top-down CPD module (1) classifies slices as “key” or “non-key”; (2) slice-wise confidence re-weighting by detection; (3) determining slice-wise ROIs for each prospective slice; and (4) curve parsing to select final key slice and corresponding ROIs.

The classifier’s goal is to identify whether each MR slice corresponds to a key slice or not. Any state-of-the-art classifier can be used, trained on “key” and “non-key” slices, and ignored “marginal” ones. Using T2-anchor method, we obtain confidence scores for each of the five sequences, $j$, and for each slice, $m$: $s_{j,m}^{\text{cls}}$. The final classification confidence score across all sequences, $s_m^{\text{cls}}$, is then computed via averaging:

$$s_m^{\text{cls}} = \frac{1}{5} \sum_{j=1}^{5} s_{j,m}^{\text{cls}}. \tag{1}$$

Since performance relies heavily on identifying key slices, building in redundancy and robustness is necessary. As a result, we enhance the classification-based confidences with scores computed from a detector. Detection produces a set of confidence values and predicted bboxes for each slice and sequence: $S_m^{\text{det}}$ and $\hat{B}_m$, respectively. We group the outputs across all sequences together:

$$S_m^{\text{det}}, \hat{B}_m = \{S_j^{\text{det}}, \hat{B}_j\}_{j=1}^{5}. \tag{2}$$

To calculate a slice-wise confidence score, we choose the maximum confidence but biased toward larger bboxes, based on the assumption that they are more diagnosable:

$$s_m^{\text{det}} = \max \left( \left\{ \left( a_{m,k} + s_{m,k}^{\text{det}} \right) / 2 \right\}_{k=1}^{\hat{K}_m} \right),$$

where $k$ indexes the predicted bboxes and confidences in $S_m^{\text{det}}$ and $\hat{B}_m$ and $a_{m,k} \in (0,1]$ is the normalized bbox area across all slices.

The next step is to select a slice-wise ROI from each prospective key slice. We use a voting scheme where for every possible pixel location we sum up the detection confidences of any bbox, $s_{m,k}^{\text{det}} \in \hat{B}_m$, that overlaps with it. We then choose the pixel location with the highest detection confidence sum. Then, for all the bboxes that overlap the chosen pixel location, we take their mean location and size as the final slice-wise ROI. Importantly, we filter out low-confidence ROIs using a threshold $t$, which is determined by examining the overlap of resulting slice-wise ROIs with ground truth bboxes in validation. We choose the $t$ that
provides the best empirical cumulative distribution function of overlaps, and thus the best balance between false negatives (FNs) and false positives (FPs).

Finally, with a classification and detection slice-wise confidence in hand, the ultimate step is to select and rank slices. First, we produce a confidence curve across all slices, using \( s_{cls}^m \), which we then parse to determine valid key-slice candidates. To do this, we identify peaks in the curve, which ideally should each correspond to the presence of a true lesion. Each peak defines a key-slice zone, which is the adjoining region where confidence values are within 1/2 of the “peak” confidence value. We also only admit slices that contain at least one bbox with a confidence score > \( t \). Only key slices in key-slice zones will be ranked and selected. Next, we combine classification and detection scores:

\[
\begin{align*}
    s_{cls+det}^m &= (s_{cls}^m + s_{det}^m) / 2.
\end{align*}
\]

From these we select the top \( T\% \) of slices. We choose \( T \) by examining the corresponding precision and recall on all validation studies, choosing the value corresponding to an average recall \( >= 0.5 \) (across all patients) and which gives a first quartile (Q1) precision of \( >= 0.6 \). This strategy is applied for all evaluated detectors. The corresponding slice-wise ROIs for the selected slices then compose the CPD key ROIs, \( \mathcal{B}^{CPD} \).

### 2.2 Localization-By-Over-Segmentation

While the CPD module is robust, it can still struggle when faced with low-contrast or small lesions. Addressing these edge cases requires a complementary strategy. As illustrated in Fig.2(c), we integrate a bottom-up LBOS module specifically tuned for small tumors.

The first challenge in LBOS is the non-availability of segmentation masks. Considering the prohibitive work-load of pixel-wise annotation, e.g., the four readers used in the LiTS dataset [3], we avoid relying on manual masks. Instead we follow a workflow similar to [6] and use GrabCut [20] to generate pseudo-masks based off of the RECIST marks.

To complement the CPD, we design the LBOS module to be biased toward high recall. To achieve this, we use the Tversky loss [21]. Using a floating point relaxation of set operations and \( k \in \Omega \) to represent the pixel domain, the loss is:

\[
\begin{align*}
    \ell_{tver} &= - \sum p_k y_k + \lambda_1 \sum p_k (1 - y_k) + \lambda_2 \sum (1 - p_k) y_k,
\end{align*}
\]

where \( p_k \) and \( y_k \) represent the floating-point prediction and binary pseudo-label, respectively. When \( \lambda_1 < \lambda_2 \), minimizing Eq.(4) will incline predictions toward high recall. A downside to this high-recall loss is that it can produce FPs far away from lesion boundaries. Similar to the boundary loss of [17], we address this by computing the distance to the nearest pseudo-mask boundary, \( d_k \), and use it to weight any errors:

\[
\begin{align*}
    \ell_{dis} &= \sum p_k (1 - y_k) d_k + \sum (1 - p_k) y_k d_k \left| \Omega \right|.
\end{align*}
\]
The final loss is the sum of $\ell_{\text{ver}}$ and $\ell_{\text{dis}}$, where we use $\lambda_1 = 0.2$ and $\lambda_2 = 0.8$.

Similar to the CPD detector, we obtain five prediction volumes corresponding to five T2-anchor sequences, $\hat{M}_j$, which are then aggregated into a voting mask $\hat{M} = \sum_{j=1}^{5} \hat{M}_j$. We then determine the highest vote value in $\hat{M}$, denoted $\tau$. This is used as a threshold to create a final binary mask. Because the LBOS module should compensate for CPD failure cases, usually small tumors, it should select key slices based on the size of tumor. We identify lesion candidates as individual 3D connected components with its length smaller than 2.5 cm. From these, we select five key slices with the highest lesion-candidate areas. Localization is straightforward: for each selected slice, we draw a minimum bounding rectangle with respect to the binary mask. This produces boxes of small tumors $B^{\text{LBOS}}$. In addition to selecting key slices, the LBOS module also provides a list of all slice indices containing lesion predictions in the binary mask, $\hat{M}$. This “master” slice index list will be important when merging the CPD and LBOS results.

**Key-Slice Parser** The complete KSP module integrates the CPD and LBOS outputs. To detect CPD failure cases, we treat the master list of slice indices from the LBOS as a high-recall “sanity check”, i.e., the key slices of the CPD should overlap with the master list. If a CPD slice passes the sanity check we use its corresponding bbox. Those slices that fail the check are filtered out to ensure the high precision of KSP. Finally the LBOS bboxes of small tumors, $B^{\text{LBOS}}$, are added to $B^{\text{CPD}}$ to achieve a high recall.

### 3 Results

**Data Collection** We collected 430 multi-phase multi-sequence MR studies (2150 volumes) from Anonymized Hospital. The selection criteria was any patient who had surgical reaction or biopsy in the period between 2006 and 2019 where T1WI, T2WI, T1WI-V, T1WI-A, and DWI sequences are available. Lesion distribution was 207, 113, and 110 patients with HCC, ICC, and metastasis, respectively. We resampled and aligned them all using the DEEDS algorithm [14]. The data was then split using five-fold cross validation, with 80%, 10%, and 20% used for training, validation, and testing, respectively. Data splitting was executed on HCC, ICC and metastasis independently to avoid imbalanced distributions. RECIST marks were labelled on each slice, under the supervision of a hepatic physician with $\geq 10$ years experience. From there, a bbox was generated. For clusters of lesions too numerous to individually mark, a bbox over each cluster was drawn, as shown in Fig.1(a).

**Implementation Details** For all experiments we augmented the data by random rotations and gamma intensity transforms. Random scaling and cropping were included for the CPD detector and classifier. All volumes were preprocessed by clipping within the 0.1% and 99.9% percentile values. The CPD classifier used a DenseNet121 backbone. Following [26], we added an additional $1 \times 1$ convolutional layer before global pooling and used log-sum-exp (LSE) pooling, finding
it outperforms the standard average pooling. Three adjacent slices are inputted to provide some 3D context. For the CPD detector, we demonstrate the benefits of our framework on three advanced detectors - 3DCE [25], CenterNet [31] and ATSS [29]. To avoid overly tuning hyper-parameters, the network structure and loss use the same settings as the original papers. For the LBOS, the standard U-Net [19] network with distance-aware Tversky loss is implemented. As for lesion characterization, we test three standard classifiers, ResNet101 [13], DenseNet121 [15] and ResNeXt101 [24], as well as two texture based classifiers, DeepTEN [28] and SaDT [16].

**Evaluation Metrics** To evaluate key slice identification, we select the top $T\%$ of slices across all studies. For each choice of $T$, we calculate the precision and recall for each study. We graph the corresponding average recall (across patients) along with the corresponding median, first quartile (Q1) and third quartile (Q3) precisions. To evaluate localization, we examine the overlap of selected ROIs against any ground truth bbox using the intersection over union (IoU). When ground truth bboxes are drawn over lesion clusters, we use the intersection over bounding box (IoBB) [22] as an IoU proxy. For each patient, we examine the average overlap across all predicted ROIs and also the worst case (lower bound overlap). We then directly observe the empirical cumulative distribution function (CDF) of these overlaps across all patients. Finally, for the overall characterization performance, we measure patient-wise accuracy, one-vs-all and mean F1 score(s) of the three tumor types, with emphasis on HCC-vs-others given its prominence in clinical work [2].

**Localization** We first evaluate how CPD and KSP can enhance three advanced detectors, which would otherwise directly output key ROIs according to their bbox confidence scores. We choose three strong baselines: CenterNet has been used to achieve state-of-the-art results in DeepLesion [5]; ATSS achieves the best performance on COCO [29]; and 3DCE is a powerful detector specifically designed for lesion localization [25].

From Fig. 3, the improvement of CPD is prominent on all detectors. CPD decreases 0.5%-3.3% patients of low overlap ($\leq 25\%$ IoU-IoBB) compared to the three detectors. The improvement of lower bound (LB) is even more significant, with around 13% fewer patients with zero overlap and 12% fewer patients with low overlap. By adding the LBOS sanity check and small-lesion bboxes, KSP further decreases the low overlap by 0.5% – 4% and achieves an overall improvement of 3% – 5% beyond pure detectors. The contribution of the KSP is most pronounced when examining the decline of patients with zero overlapping ROIs with the ground truth, with a further decrease of 2% – 6% on average and 1%–6% on the lower bound compared with CPD. Tackling these uncommon edge cases is the very reason for integrating the bottom-up LBOS module. Occasionally, LBOS produces ROIs with moderate overlap (50%-60% IoU-IoBB) with the ground truth, as shown in the figure of CenterNet and 3DCE, causing the CDF curves of CPD to look better than those of KSP in the interval of [50%, 60%]
Fig. 3. CDF curves of three detectors and their counterparts of KSP on test set. Solid curves demonstrate the average ROIs overlap across selected slices in each patient, while dashed curves show the lowest overlap (denoted by “LB”). Tables show exact percentages of patients with average or lowest overlap <= 0, 0.25 or 0.5. The lower percentage indicates the better performance.

overlap. However, we note that when the localized ROIs have an overlap beyond 40% with the ground truth, they are generally already good enough to make a diagnosis. Thus it is more impactful to decrease poor-quality ROIs (<= 25% IoU-IoBB) than to boost a 50% overlap to 80% or higher. Thus, the LBOS sanity check and bboxes successfully enhances the robustness of localization, which is critical for viable clinical CAD solutions.

Characterization According to Fig. 3, CenterNet with KSP surpasses 3DCE and ATSS in average and LB overlap, respectively. Therefore, we choose it as our KSP detector and evaluate various classification networks. Patient-wise diagnoses are produced by averaging classifications from detected ROIs weighted by confidence. As demonstrated in Table 1 compared with purely using classification networks, KSP significantly improves accuracy (+5%), mean F1 (+9%-12%) and HCC F1 scores (+2%-10%). SaDT [16] garners the highest HCC vs. others F1 score of 0.804, which is comparable to reported physician performance (0.791) [2]. Traditional radiomics method usually under-performs deep learning methods with a large margin, especially compared to our method.
Table 1. Comparison of different characterization methods. Radiomics is implemented based on the manual localization and SaDT\cite{16} cannot be used without ROIs.

| Methods                  | Accuracy   | mean F1     | F1(HCC)   | F1(ICC)   | F1(Meta.)   |
|--------------------------|------------|-------------|-----------|-----------|-------------|
| Radiomics                | 58.65 ± 4.51 | 55.07 ± 6.34 | 71.37 ± 4.05 | 39.50 ± 10.94 | 54.36 ± 0.26 |
| ResNet101 [13]           | 59.54 ± 3.53 | 50.03 ± 3.55 | 76.85 ± 4.55 | 12.74 ± 8.58 | 60.51 ± 4.55 |
| DenseNet121 [25]         | 61.68 ± 5.43 | 51.24 ± 3.73 | 75.91 ± 10.37 | 17.54 ± 14.51 | 50.15 ± 7.57 |
| ResNeXt101 [24]          | 60.51 ± 5.32 | 54.96 ± 5.60 | 78.15 ± 6.01 | 27.62 ± 11.89 | 59.12 ± 6.79 |
| DeepTEN [28]             | 53.97 ± 3.38 | 54.74 ± 3.12 | 65.03 ± 6.60 | 41.39 ± 5.63 | 57.80 ± 6.40 |
| KSP+ResNet101            | 64.51 ± 4.35 | 60.75 ± 3.67 | 76.05 ± 6.34 | 45.83 ± 4.12 | 60.37 ± 5.49 |
| KSP+DenseNet121          | 66.61 ± 2.33 | 63.28 ± 1.78 | 77.71 ± 3.25 | 50.02 ± 7.39 | 62.11 ± 5.29 |
| KSP+ResNeXt101           | 67.56 ± 3.90 | 63.30 ± 4.06 | 80.18 ± 2.68 | 46.78 ± 4.65 | 62.95 ± 9.61 |
| KSP+DeepTEN              | 66.34 ± 2.40 | 63.32 ± 3.06 | 75.99 ± 4.30 | 52.27 ± 12.02 | 61.71 ± 6.68 |
| KSP+SaDT                 | **67.79 ± 3.82** | **63.79 ± 3.71** | **80.35 ± 4.01** | 49.84 ± 7.80 | 61.19 ± 6.07 |

Fig. 4. PR curves of three key slice selection strategies. For each choice of top \( T \)\% of slices selected for each study, we graph the corresponding average recall (across all patients) and the first quartile (Q1), median (M), and third quartile (Q3) precisions.

**CPD Ablation Study** We validate that detection-based reweighting and curve parsing (CP) can better select key slices compared with detection module alone. To do this, we select key slices based on 1) directly using detection output, 2) using \( s_{cls+det} \) of Eq. 3, and 3) using CP on \( s_{cls+det} \). In Fig 4, detection-based reweighting significantly outperforms detection, with the biggest gains in boosting Q1 precisions, thus ensuring that lower-bound precisions are much higher. Once CP is applied, it provides better precision and recall no matter which detector we use, indicating that parsing the confidence curves can help much more reliably identify key slices. To make decision on top \( T \)% slices, we choose the percentage with the average recall \( > 0.5 \) and Q1 precision \( > 0.6 \) for CenterNet, ATSS, and 3DCE, which are 48%, 54%, and 50% respectively.

4 Discussion and Conclusion

As progressing toward more clinically viable CAD, research efforts will increasingly focus on developing truly reliable and robust solutions. We contribute
toward this goal for the liver lesion characterization. Specifically, we articulate a physician-inspired approach toward ROI localization that breaks down the complex problem into key-slice identification, and then localization. Using a combination of CPD and LBOS, our KSP realization can achieve very high robustness, with 85% of its ROIs having an overlap of \( \geq 40\% \). Overall, our fully automated CAD solution can achieve an HCC-vs-others F1 score of 80.4%. Importantly, this performance is reported on histopathologically-confirmed cases, which selects for the most challenging cases requiring CAD intervention. Even so, this matches reported clinical performances of 79.1% [2], despite such studies including both radiologically and histopathologically-confirmed cases. Given the challenging nature of liver lesion characterization, our proposed CAD system represents an important step forward toward more clinically practical solutions.

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