Machine learning for automated and real-time two-dimensional to three-dimensional registration of the spine using a single radiograph

Andrew Abumoussa, MD, MSc, Vivek Gopalakrishnan, MS, Benjamin Succop, BS, Michael Galgano, MD, Sivakumar Jaikumar, MD, MS, Yueh Z. Lee, MD, PhD, and Deb A. Bhowmick, MD

OBJECTIVE The goal of this work was to methodically evaluate, optimize, and validate a self-supervised machine learning algorithm capable of real-time automatic registration and fluoroscopic localization of the spine using a single radiograph or fluoroscopic frame.

METHODS The authors propose a two-dimensional to three-dimensional (2D-3D) registration algorithm that maximizes an image similarity metric between radiographic images to identify the position of a C-arm relative to a 3D volume. This work utilizes digitally reconstructed radiographs (DRRs), which are synthetic radiographic images generated by simulating the x-ray projections as they would pass through a CT volume. To evaluate the algorithm, the authors used cone-beam CT data for 127 patients obtained from an open-source de-identified registry of cervical, thoracic, and lumbar scans. They systematically evaluated and tuned the algorithm, then quantified the convergence rate of the model by simulating C-arm registrations with 80 randomly simulated DRRs for each CT volume. The endpoints of this study were time to convergence, accuracy of convergence for each of the C-arm’s degrees of freedom, and overall registration accuracy based on a voxel-by-voxel measurement.

RESULTS A total of 10,160 unique radiographic images were simulated from 127 CT scans. The algorithm successfully converged to the correct solution 82% of the time with an average of 1.96 seconds of computation. The radiographic images for which the algorithm converged to the solution demonstrated 99.9% registration accuracy despite utilizing only single-precision computation for speed. The algorithm was found to be optimized for convergence when the search space was limited to a ± 45° offset in the right anterior oblique/left anterior oblique, cranial/caudal, and receiver rotation angles with the radiographic isocenter contained within 8000 cm³ of the volumetric center of the CT volume.

CONCLUSIONS The investigated machine learning algorithm has the potential to aid surgeons in level localization, surgical planning, and intraoperative navigation through a completely automated 2D-3D registration process. Future work will focus on algorithmic optimizations to improve the convergence rate and speed profile.

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KEYWORDS machine learning; spine; registration; digitally reconstructed radiograph; DRR

OPERATIVE level localization with accurate and precise three-dimensional (3D) registration for surgical navigation is a necessary step for successful and safe navigated surgery of the spine. Specifically, identification of the correct level for intervention is an essential tenet of spine surgery. Unfortunately, errors in identifying operative levels do occur.1,2 Although the reported incidence is low (0.09–4.5 instances per 10,000 surgeries based on claims data research), nearly 50% of surveyed neurosurgeons have reported performing wrong-level spinal surgery at least once in their career.1,3 Incorrect level identification is often attributed to a lack of uniquely identifiable radiographic landmarks (especially the thoracic spine, which carries the highest incidence of these errors),
variable transitional anatomy, and the susceptibility of conventional level counting to human error.4,5 Similarly, surgical navigation relies on multiple factors for its accuracy and has also been found to be least accurate in the thoracic spine.6 Assessing the accuracy of navigated techniques remains challenging, as radiographic and clinical assessments vary across spinal segments and have variable interrater reliability.7 Current navigation systems to the patient.9 Minimally invasive navigated thoracic screw placements have a variably reported accuracy in the variable interrater reliability.7 Current navigation systems rely on appropriate registration of bony landmarks and continuous optical tracking of reference arrays attached to the patient.9 Minimally invasive navigated thoracic screw placements have a variably reported accuracy in the literature along with a 10% experimental rate of medial breaches when utilizing current technologies according to a recent systematic review and cadaveric study.8

Automatic localization and reregistration via machine learning and computer vision represent potential tools to mitigate these issues.4,6 Prior work has evaluated the registration of a two-dimensional (2D) projection image to a 3D volume with the algorithmic goal of estimating the transformations from the 2D geometry to the 3D volume coordinate system.9,10 Potential machine learning solutions to address the 2D-3D registration problem are divided into manually trained feature-based approaches, which require expert segmentation for model construction, or signal intensity–based algorithms.9 Segmentation models have several drawbacks: susceptibility to parameter tuning errors, overfitting, segmentation errors, and significant data labeling requirements.9,11–13 Intensity-based approaches function by aligning signal intensities between 2D and 3D modalities.14–17

Our work evaluates the properties of the unconstrained, uncalibrated, self-supervised 2D-3D alignment problem with machine learning via an intensity-based approach. The potential to alleviate the need for supplemental camera visualization and human verification during surgery, while enabling instant reregistrations, would improve operative efficiency and accuracy.

**Methods**

**Patient Population and Radiographic Database**

Data used for this analysis were the pooled collection of unique studies from the public VerSe 2019: Large Scale Vertebrae Segmentation Challenge repository.18–20 This data set includes spinal imaging from subjects older than 18 years of age and contains CT images of the spine showing at least 7 full vertebrae. These CT scans have a minimal spatial resolution of 1.5 mm in the craniocaudal direction and 1 mm in the anteroposterior direction. Notably, this data set excludes traumatic fractures and bony metastases but includes osseous changes such as Schmorl nodes, hemangiomas, degenerative changes, and foreign material from prior treatments (e.g., kyphoplasty spondylodesis). Our final data set included CT scans from 127 patients with 150 anatomical variants (e.g., thoracolumbar or lumbosacral transition vertebra, cervical or lumbar ribs, hemivertebra, etc.). Table 1 provides the anatomical distribution and volumetric properties of these scans. No clinical or demographic information was analyzed. No examinations were excluded.

In accordance with the institutional review board guidelines for the University of North Carolina Hospitals, a waiver of consent was utilized since this is a public and anonymized data set.

**Experimental Design**

Our experiments were designed to test the hypothesis that any fluoroscopic image (referred to as the “initial pose”), regardless of orientation, could be registered to its associated CT scan by identifying the values of the 6 degrees of freedom (6DoF) of a C-arm required to reproduce a target image. Specifically, we defined the 6DoF for a virtual C-arm as follows: θ, as the degrees in the right anteroposterior oblique/left anterior oblique (RAO/LAO) plane; φ, as the degrees in the cranial/caudal plane; γ, as rotation of the receiver; and x, y, and z Cartesian planes, as a measure of the degree between the virtual C-arm’s isocenter and the volumetric center of the CT volume (Fig. 1). These values would be converted to a vector, p = (θ, φ, γ, x, y, z), that parameterizes the pose of the virtual C-arm relative to the CT volume, resulting in a unique fluoroscopic projection obtained with a C-arm in that exact orientation.

To test our hypothesis, we used the VerSe 2019 CT data sets and a digitally reconstructed radiograph (DRR) generator to simulate fluoroscopic C-arm captures at random positions. Many algorithms exist to generate a DRR from CT volumes.16,21–26 For this work, we used DiffDRR, a DRR generator written in PyTorch, to leverage the auto-differentiable optimization schemes common in machine learning frameworks.16

We began this work by evaluating the properties and limitations of the negative zero-normalized cross-correlation (ZNCC) as a proposed loss function.27,28 In signal processing, the cross-correlation is a measure of similarity between two signals. We methodically quantified the image similarity of two DRRs, one of which was the stationary target and the other a moving DRR for which we systematically changed each of the 6DoF parameters to create an updated image. This experiment was designed to demonstrate the convexity of the loss function and its range and rates of convergence for the arbitrarily chosen orthogonal posteroanterior (PA) and lateral projections. The ultimate outcome was a formal evaluation of the neg-

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**TABLE 1. Summary of study statistics analyzed from the VerSe 2019 data set**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total FOV *</td>
<td>8</td>
</tr>
<tr>
<td>Cervical</td>
<td>49</td>
</tr>
<tr>
<td>Thoracic</td>
<td>102</td>
</tr>
<tr>
<td>Lumbar</td>
<td></td>
</tr>
<tr>
<td>CT dimensions (cm) †</td>
<td></td>
</tr>
<tr>
<td>x</td>
<td>26.0 ± 11.2</td>
</tr>
<tr>
<td>y</td>
<td>32.6 ± 12.5</td>
</tr>
<tr>
<td>z</td>
<td>46.4 ± 18.6</td>
</tr>
</tbody>
</table>

FOV = field of view.
* Total FOV indicates the number of studies in which the cervical, thoracic, or lumbar vertebrae were contained within the image volume’s FOV.
† Values are expressed as average ± standard deviation.
The parameter diagram shows the 6DoF that we aim to retrieve with our work. The large black dot in the middle is the radiographic center of the imaged volume. We aim to compute the displacements in the x, y, and z planes between the volumetric center and the fluoroscopic isocenter (cm) and cranial/caudal (\(\phi\)), RAO/LAO (\(\theta\)), and receiver’s rotational (\(\gamma\)) angles.

Convergence Rate

With the hyperparameters of our algorithm defined, we evaluated the convergence rate for the largest CT scan by volume not in the training set. Specifically, we explored the likelihood of convergence, as well as the speed of convergence, using a single study and 500 simulated projections in both the PA and lateral planes each, for a total of 1000 experiments. The largest CT scan in our data set that captured the complete cervical, thoracic, and lumbar spine was used. The CT volume was split into a collection of \(20 \times 20 \times 20\)-cm\(^3\) subvolumes, and these were used as the seeds for the simulated registrations. If the algorithm was able to determine the 6 displacement parameters with a negative ZNCC less than or equal to \(-0.999\) for a random radiographic projection, it was considered registered. Registration of a particular image was considered a failure if the moving DRR did not converge in 250 iterations. We limited the random displacements to the range of \(\pm 45^\circ\) for the \(\theta\), \(\phi\), and \(\gamma\) parameters and \(\pm 20\) cm for the \(x\), \(y\), and \(z\) parameters based on our analysis of the negative ZNCC image similarity metric.

Final Experiment

Each of the 127 scans were then read into our system as a Neuroimaging Informatics Technology Initiative (NIfTI) data set and aligned in the appropriate anatomical PA and lateral orientations. Forty random fluoroscopic images were generated by altering the 6DoF for both the PA and lateral projections (80 total fluoroscopic shots for each 3D volume), and we evaluated the performance of our 2D-3D machine learning registration algorithm.

Performance Analysis

The performance of our algorithm is reported when utilizing a CUDA-accelerated DRR generator (NVIDIA Corp.). Graphics processing unit (GPU) benchmarks were run on an NVIDIA Titan RTX connected via Thunderbolt 3 as an eGPU to a 2020 Apple MacBook Pro equipped with a 2.3-GHz quad-core Intel Core i7 processor with 32 GB of low-power double data rate (LPDDR4x) random access memory (RAM).

Results

Synthesized DRRs were generated using Siddon’s ray-tracing algorithm;\(^{29}\) we visualized each CT scan in the sagittal, coronal, and axial planes with the associated ground truth DRRs in both the PA and lateral views (Fig. 2). We chose to simulate resultant DRRs using a typical 30\(\times\)30-cm receiver with a pixel spacing of 1.5 mm, resulting in a 200 \(\times\) 200–pixel receiver image. Simulated DRR resolutions can be increased to improve anatomical detail or decreased to minimize computational times as needed.

With a system in place capable of taking a CT scan and generating DRRs, we explored the problem of solving for the 6DoF registration parameters. Namely, given a DRR,\(_{\text{init}}\) defined by the function \(\eta_{\text{initial}}(CT, \theta, \phi, \gamma, x, y, z)\), we wanted to identify the exact displacement parameter set \(\delta = (\delta_\theta, \delta_\phi, \delta_\gamma, \delta_x, \delta_y, \delta_z)\) that transforms DRR\(_{\text{initial}}\) to the ground truth such that DRR\(_{\text{target}} = \eta_{\text{target}}(CT, \theta + \delta_\theta, \phi + \delta_\phi, \gamma + \delta_\gamma, x + \delta_x, y + \delta_y, z + \delta_z)\). Our algorithm returns the displacement set \((\delta_\theta, \delta_\phi, \delta_\gamma, \delta_x, \delta_y, \delta_z)\) via gradient descent. One convergence sequence (iteration) is shown in Fig. 3.

Our evaluation of the negative ZNCC surface map was done by conducting a comprehensive simulation study. A CT scan was chosen at random, and we generated both PA and lateral projections. We methodically displaced the virtual C-arm across an unconstrained field of view (180\(^{\circ}\) in both the \(\theta\); RAO/LAO and the \(\phi\); cranial/caudal angles) and...
FIG. 2. DRR synthesis. We demonstrate the fields of view for 3 imported CT scans (rows A–C) in the axial, sagittal, and coronal planes (columns D, E, and F, respectively). Columns G and H are digitally reconstructed radiographs in the classic PA and lateral projections for the cervical, thoracolumbar, and lumbar spine at 200 × 200–pixel resolution simulating a 30 × 30–cm receiver with a 1.5-mm pixel spacing.

FIG. 3. Auto-differentiable pose estimation. A: The algorithm iteratively aligns a random initial pose (DRR<sub>moving</sub>) to a target PA (DRR<sub>target</sub>) view. Using gradient descent along the negative ZNCC loss function, we identify the exact displacement required of a C-arm to reproduce the target image. B: Radiographs at selected iterations as the algorithm solves the registration problem. Numbers represent algorithmic iterations.
± 40 cm in any direction from the volume center. We noted that negative ZNCC is locally convex when near the correct solution (Fig. 4). This confirmed that negative ZNCC is an appropriate loss function to be optimized by gradient descent when aligning a pair of DRRs. We also noted that there is a range around the global minimum where negative ZNCC can incorrectly converge to local minima, namely when the radial displacement is > 45° along the θ or φ angles or distances > 20 cm along any of the x, y, or z planes. This observation provided the 6DoF parameter perturbation bounds for our future experiments (Fig. 5).

Hyperparameter tuning was performed using a grid search (Fig. 6). We varied the learning rates for the translation and rotation parameters independently, as they utilize different units of measurements and scales. Our grid search was performed over the range of 10⁻⁵ to 10³. 

FIG. 4. Methodical evaluation of negative ZNCC surface map. This figure shows the shape of the negative ZNCC curves with respect to changes along each set of parameters. A: In the unconstrained global search, we note local divergence from the optimal solutions when sufficiently large displacements between the target and moving DRRs have occurred. B: The local negative ZNCC surface maps all demonstrate a convex convergence to a single true solution, indicating that it is an appropriate loss function to optimize. Contour maps on the floor of each chart demonstrate minimum differences in blue and maximum differences in red. Our algorithm traverses these maps to align each pair of images.
Measuring the rates and speeds of convergences, we found that the optimal hyperparameters for our algorithm were learning rates of $4.5 \times 10^{-2}$ for the rotational parameters and $7.5 \times 10^1$ for the translational parameters. Gradient descent with a momentum was utilized to avoid an arrest at a local minimum with the optimal momentum of 0.60 and dampening of 0.45 identified through a grid search. We found these parameters to be the same for PA and lateral registrations resulting in the greatest percentage of studies converging with the least number of iterations needed (Fig. 7). The grid search was performed using a subset of 5 CT scans from the original data set. Each combination of...
parameters was tested with 50 randomly generated DRRs from these 5 CT scans (10 DRRs per CT scan).

2D-3D registration using a single fluoroscopic image was tested using the largest CT scan in the data set that captured the complete cervical, thoracic, and lumbar spine. We generated 500 PA and 500 lateral projections and measured the convergence statistics for 1000 simulations for this CT volume. Figure 3 and Video 1 demonstrate a single experimental sequence for a successful convergence in which we align a random initial pose to a target view by computing the 6DoF necessary to transform the initial pose to the target view.

**VIDEO 1.** Clip showing an animated graphics interchange format (GIF) providing visualization of a random convergence run. The stationary target projection represents the surgeon’s desired fluoroscopic projection. The animated frame starts with a random orientation of the virtual C-arm. Our algorithmic alignment then updates each frame with the calculated projection as it identifies the 6DoF transformations necessary to align the virtual C-arm to the target projection. © Andrew Abumoussa, published with permission. Click here to view.

A set of example random displacements are shown in Fig. 5 for the PA and lateral views. We found that our algorithm converged for both PA and lateral projections with a success rate of 83% and 81%, respectively, in an average of 2.09 ± 0.88 seconds requiring an average 33 ± 23 iterations for this single CT volume (Fig. 7). When we performed the pooled evaluation, we generated 80 fluoroscopic views (40 lateral and 40 PA views) for each CT scan. A total of 10,160 fluoroscopic projections from the 127 CT scans were simulated with similar results: average time to convergence was 1.96 ± 1.54 seconds requiring on average 51 ± 41 iterations over the data set.

**Discussion**

There are limitations to current surgical technologies that utilize 2D-3D image registration for planning and navigation purposes: these systems rely on surgeon setup and confirmation and require unobstructed lines of sight to tracked hardware, intraoperative CT scans increase operative times, and inaccuracies accumulate as distance increases from a system’s reference array. 30–32 2D-3D registration via machine learning has the potential to address these pitfalls, especially if encapsulated in a completely automated, self-supervised, real-time algorithm.

Operative efficiency is critical to spine surgery, as a decreased operative time has been shown to directly reduce the surgical site infection risk.33,34 For most 3D image-based navigation systems, the displacement of a reference array relative to the patient following registration necessitates a repeat CT scan. This extends procedural and operative times while also introducing additional radiation exposure.31 Both the incidence of and operative-time penalty for these technical errors are not well described in the literature. One study comparing a computer vision–based reregistration to traditional CT registration has reported a 7% incidence of reregistration for CT-based navigation.35 A comparison of fluoroscopic guidance with CT guidance has suggested that the average operative time increases by 30 minutes for CT-based navigation, which is concordant with our institution’s experience.36

Prior works have described constrained, calibrated, or supervised models that are unable to address the unconstrained, uncalibrated, unsupervised search.9–17,37,38 Otake et al. presented a constrained, calibrated, and unsupervised signal intensity–based 2D-3D registration system able to solve the alignment problem when the 6DoF only varied by 50 mm in the x plane, 150 mm in the y plane, and 100 mm in the z plane, with only 10° angular variability for a C-arm following calibration.37 Varnavas et al. presented a constrained, uncalibrated, supervised algorithm that requires manual identification of vertebral bodies by a user preoperatively before being able to perform the registration task.10 In addition, this algorithm had limited accuracy, as it could only register intraoperative fluoroscopy images to the discrete set of preoperatively segmented levels. In con-
trast, our work methodically evaluates a machine learning algorithm’s ability to perform a completely automated 2D-3D alignment in an unconstrained global search.

To avoid overfitting, we systematically tuned the machine learning algorithm with two separate learning rates as described in Methods. We found that there was a broad range of learning rates that provided maximum likelihoods of convergence (Fig. 7). We tuned the hyperparameters for the gradient descent algorithm to accelerate the convergence via a similar grid search. While tuning these parameters, we noted the same performance for the arbitrarily chosen PA and lateral projections during validation, meaning that this work can easily be extended to converge to any projection of a surgeon’s choosing. Future work will explore other methods of tuning these parameters to guarantee the best possible performance.

We methodically assessed the surface map for our chosen loss function, ZNCC, as this function only returns 1.0 if a moving DRR is identical to the stationary DRR. By defining convergence to be 99.9% accuracy, our algorithm could only accept a solution if the alignment metrics for each parameter were >99.9% correct. We noted that this condition on the ZNCC for our machine learning algorithm resulted in divergence from the correct solution when the search space was too large. We found that the optimal search space for our intensity-based loss function was ±45° for the θ, φ, and γ parameters and ±20 cm for the x, y, and z parameters. A global unconstrained search could be performed using multiple parallel executions through the entire volume. In other words, a 20 × 40 × 40–cm³ CT volume could be searched with 4 parallel processes that exhaust the volumetric space as they independently search their respective 20 × 20 × 20–cm³ fields of view. These limitations are believed to be appropriate given the surface map of the loss function’s shape and are inherent to the machine learning algorithm. Other loss functions exist (root mean squared error, peak signal-to-noise ratio, structural similarity index measure) when comparing image similarity between DRRs, which we intend to evaluate in planned future cadaveric work.

Our reported convergence rate was 82% during our simulated experiments of 10,160 x-rays using 127 different CT scans. It is important to note that the convergence rate is not the success rate of the algorithm; instead, it states that starting with any randomly oriented radiographic pose capturing any portion of a CT volume, our algorithm can traverse the similarity gradient to obtain the correct alignment without any algorithmic optimizations. This seems appropriate for this problem, as a global search increases computational complexity and memory requirements significantly, whereas other models that use convolutional neural networks that utilize feature-based registrations or preconstrained searches have limited generalizability to align new CT scans.

Limitations and Future Directions

This work assessed the feasibility of machine learning to automatically perform 2D-3D registration in a reliable, automated, self-supervised fashion. This framework could empower surgeons with improved safety profiles and operative efficiency, although there are limitations that must be addressed before adoption into the surgical armamentarium.

We note the concern over the times required for convergence cited in prior work. 37,38,41 We do not believe that a 2-second convergence presents a significant limitation within typical surgical workflows. The fastest commercial system requires 20 seconds for reregistrations. 42,43 Furthermore, information from prior alignments can seed the search for subsequent fluoroscopic captures. Our algorithm can generate one full-resolution digital radiographic projection and perform a gradient descent iteration in 27 msec on a single modern consumer graphics card. Multiple optimizations will be implemented in future work for live fluoroscopy registration at 15 fps, such as tiered resolution searches and sparse sampling of the DRR rendering to reduce the computational times.

Furthermore, this work represents a simulated radiographic experiment utilizing one machine learning algorithm. This work is not a comprehensive evaluation of all possible loss functions, nor is it a systematic comparison of other possible machine learning solutions. It is important to understand the reliance of the DRR generator used to create the fluoroscopic projections, as that is the input being used for the image similarity metric. Because we are ultimately comparing the image similarity of two synthetic radiographs, future work is aimed at validating the accuracy of this technique when comparing a DRR to an actual fluoroscopic image. Image artifact and radiographic scatter introduced by operating tables and surgical instruments are also anticipated to further degrade the image similarity, and their collective effects on the machine learning algorithm must be explored. To address and evaluate these limitations, a cadaveric study is planned to explore the computational similarity in an in vitro model.

Finally, all patients were supine during these CT acquisitions. This algorithm is performing a rigid alignment and has not been generalized to process deformable registrations capable of accounting for changes in anatomical alignment that may occur with unstable fractures or certain surgical maneuvers. Although the limitations of a rigid registration can be mitigated by utilizing an intraoperative scan following positioning, our goal with future work is to incorporate deformable registration techniques into a generalized form of this algorithm.

With these results, we hope to lay the foundation for solutions that empower surgeons with efficient, continuous surgical registrations via simple fluoroscopy. Machine learning can potentially impact multiple aspects of spine surgery whether by providing surgeons with intuitive overlays to assist with localization, using our alignment algorithm to provide any desired radiographic projection needed, or potentially mechanically aligning operative C-arms to obtain desired views. Instant reregistration with each fluoroscopic acquisition could address the accumulating errors in traditional CT-based navigation. The accuracy, speed, and automated convergence make this a powerful tool for spine surgeons.

Conclusions

Our model effectively provides an instant and automat-
ed solution for 2D-3D image registration utilizing DRRs and associated CT volumes with high convergence (82%) and accuracy (99.9%). This technique can improve both the safety and efficiency profile for spine surgery by potentially providing surgeons with instant alignment and continuous registration for surgical procedures. Further work is needed to incorporate deformable registration to account for the anatomical shifts that occur with patient positioning or surgical maneuvers.

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References


**Disclosures**

Dr. Lee reports royalties from Xinvisio LLC outside the submitted work. Dr. Bhowmick reports personal fees from Medtronic PLC and SpineWave LLC, outside the submitted work.

**Author Contributions**

Conception and design: Abumoussa, Gopalakrishnan, Jaikumar, Lee. Acquisition of data: Abumoussa, Jaikumar. Analysis and interpretation of data: Abumoussa, Gopalakrishnan, Succop, Jaikumar, Lee, Bhowmick. Drafting the article: Abumoussa, Succop, Jaikumar. Critically revising the article: Abumoussa, Gopalakrishnan, Succop, Jaikumar, Lee, Bhowmick. Reviewed submitted version of manuscript: Abumoussa, Gopalakrishnan, Succop, Galgano, Bhowmick. Approved the final version of the manuscript on behalf of all authors: Abumoussa. Statistical analysis: Abumoussa, Gopalakrishnan. Administrative/technical/material support: Abumoussa, Lee. Study supervision: Abumoussa, Galgano, Lee, Bhowmick.

**Supplemental Information**

**Videos**


**Correspondence**

Andrew Abumoussa: University of North Carolina at Chapel Hill Hospital, Chapel Hill, NC. andrew@med.unc.edu.