Three-dimensional–printed marker–based augmented reality neuronavigation: a new neuronavigation technique

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OBJECTIVE The aim of this study was to assess the precision and feasibility of 3D-printed marker–based augmented reality (AR) neurosurgical navigation and its use intraoperatively compared with optical tracking neuronavigation systems (OTNSs).

METHODS Three-dimensional–printed markers for CT and MRI and intraoperative use were applied with mobile devices using an AR light detection and ranging (LIDAR) camera. The 3D segmentations of intracranial tumors were created with CT and MR images, and preoperative registration of the marker and pathology was performed. A patient-specific, surgeon-facilitated mobile application was developed, and a mobile device camera was used for neuronavigation with high accuracy, ease, and cost-effectiveness. After accuracy values were preliminarily assessed, this technique was used intraoperatively in 8 patients.

RESULTS The mobile device LIDAR camera was found to successfully overlay images of virtual tumor segmentations according to the position of a 3D-printed marker. The targeting error that was measured ranged from 0.5 to 3.5 mm (mean 1.70 ± 1.02 mm, median 1.58 mm). The mean preoperative preparation time was 35.7 ± 5.56 minutes, which is longer than that for routine OTNSs, but the amount of time required for preoperative registration and the placement of the intraoperative marker was very brief compared with other neurosurgical navigation systems (mean 1.02 ± 0.3 minutes).

CONCLUSIONS The 3D-printed marker–based AR neuronavigation system was a clinically feasible, highly precise, low-cost, and easy-to-use navigation technique. Three-dimensional segmentation of intracranial tumors was targeted on the brain and was clearly visualized from the skin incision to the end of surgery.

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KEYWORDS neuronavigation; augmented reality; 3D-printed marker

INTRAOPERATIVE image guidance has been a necessity in neurosurgical operations for the past 2 decades for localizing the pathology. Preoperative and intraoperative determination of the shape, localization, size, and 3D structure of intracranial pathologies (e.g., primary or secondary tumors, vascular pathologies, hydrocephalus, and epileptic focus) gives significant advantage for resection of the pathology without any injury to adjacent important structures, in order to prevent neurological deficit and improve patient survival. In this sense, the term “neuronavigation” has been introduced to fully reveal the size, shape, and location of the mass and has gained importance with the help of investments in technology. Neuronavigation in the surgery of intracranial pathologies started with stereotactic frame-based surgery at the end of the 20th century¹ and has evolved into computer-based surgical planning

with the progress of software and hardware developments in the 21st century.^{2–4} In the current clinical routine and surgical training, surgical planning is achieved based on important landmarks in the skull or superficial skin anatomy. Commercially available neuronavigation systems with infrared cameras are essential tools in neurosurgery operations all over the world. However, these systems are high cost, time-consuming, and have some physical limitations; they are difficult to use with the patient in prone and lateral positions, have a long registration time, and require the viewing of a separate screen that is away from the surgical field.⁵

In this study, we developed a new method, a 3D-printed marker–assisted augmented reality (AR) neuronavigation, using mobile devices that can recognize the specific designed target on the patient’s skull. This provides 3D im-

ABBREVIATIONS AR = augmented reality; FDM = fused deposition modeling; OTNS = optical tracking neuronavigation system.

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TABLE 1. Patient demographics, and tumor localization and histopathology

	Value
Mean age, yrs	62.1 ± 14.6
Sex, F/M	1:1.6
Symptoms	
Headache	4 (50)
Neurological deterioration	2 (25)
Weakness	1 (12.5)
Seizure	1 (12.5)
Surgery position	
Supine	5 (62.5)
Lateral	2 (25)
Prone	1 (12.5)
Tumor location	
Frontal	4 (50)
Temporal	2 (25)
Occipital	1 (12.5)
Orbital	1 (12.5)
Histopathology	
Metastasis	3 (37.5)
Glial	2 (25)
Low grade	1 (12.5)
High grade	1 (12.5)
Meningioma	2 (25)
Abscess	1 (12.5)

Values represent the number of patients (%) or mean ± SD unless indicated otherwise.

age fixation on the patient's head and can show the real pathology, with the adjacent structures, in 3D and real time. Three-dimensional marker-registered pathology segmentations can be shown on the skin of the patient, and intraoperatively on the cranium and cortex, with high accuracy and ease at all stages of the operation by using 3D segmentation techniques. In this way, dependence on high-cost neuronavigation systems will decrease and the

time required for preoperative registration of images can be shortened. The AR neuronavigation can become more efficient during the surgery, and postoperative early and late complications can decrease while survival of patients can increase, due to total excision of the pathology without any injury to adjacent vascular and neural structures.⁶

Methods

Study Participants

Included in this study were 8 patients aged 18 years or older who were referred to the Ege University neurosurgery department between November 2020 and March 2021 with a diagnosed intracranial lesion seen on preoperative MR images that was suspicious for an intracranial primary or secondary tumor or abscess. Institutional review board approval was obtained. Patients who were neurologically at risk were excluded due to the additional time required for image processing. Written informed consent was obtained from all patients. Patient demographic information and localization of the tumors are described in Tables 1 and 2.

Three-Dimensional Marker Design and 3D Printing

The material used as a marker in patients was designed in the Fusion 360 (Autodesk Inc.) program as a cuboid object (30 × 30 × 30 mm) using the Model Target Generator for Unity Vuforia Engine version 8.5.9 (PTC Inc.). Fusion 360 is cloud-based computer-aided design program that allows for the manipulation and design of 3D objects. This cuboid object was introduced with the Vuforia Model Target Generator (version 9.6.3; PTC Inc.) using separate, photometrically recognized images on 5 sides, a technique that has been previously demonstrated.⁷ A triangular prism-shaped support was placed at the bottom of the cuboid object with the Fusion 360 program, and this support was fixed to a 3D-printed frame (Fig. 1B). The cuboid object was printed with a fused deposition modeling (FDM) 3D printer (Creality3D Ender-3 Pro, Creality 3D) with polylactic acid material to be used preoperatively as a cuboid marker. We designed another cuboid marker with the Model Target generator with two colors using a dual extruder 3D printer. This two-colored object (Fig. 1A) can

TABLE 2. Tumor localization and histopathology, and marker-based AR neuronavigation shift measurements compared with OTNSs

Patient No.	Tumor Localization	Pathology	Mean AR Neuronavigation Shift vs OTNS (mm)	Preop Surgical Planning + Preop AR Neuronavigation Registration (mins)
1	Rt frontal	Glioblastoma, WHO grade IV	2.48	43 + 1
2	Rt temporo-orbital	Meningioma, WHO grade II	2.75	38 + 1
3	Bilat occipital	Metastasis, atrial myxoma	1.0	40 + 1
4*	Lt orbital	Metastasis, adenocarcinoma	0.75	34 + 1
5	Rt temporal	Oligodendroglioma, WHO grade II	1.90	38 + 1
6	Lt frontal	Meningioma, WHO grade II	0.50	26 + 1
7	Lt frontoparietal	Abscess	1.50	38 + 1.2
8	Rt frontal	Metastasis, adenocarcinoma	1.63	28 + 1
Mean			1.56	35.63 + 1.02

* In this case, the OTNS had 5 mm of targeting error compared with the real localization of the pathology.

FIG. 1. Three-dimensional-printed markers for surgical planning. **A:** A dual-color printed marker for surgical planning, head positioning, surgical positioning, and intraoperative neuronavigation to be fixed to the frame. **B:** The frame to be fixed to the skin of the patient (forehead or vertex, according to the operation position). **C:** Imaging marker for MRI, filled with copper sulfate, and T1 hyperintense contrast used in stereotactic frames. **D:** Imaging marker for CT imaging filled with the contrast agent iohexol (noted as “BT”).

be sterilized in ethylene oxide gas sterilization for heat-sensitive materials and can be used intraoperatively. We used this cuboid marker intraoperatively without needing to remove the frame at the forehead.

A separate object with a triangular prism space of the same size and shape and compatible with the previously printed frame was designed and produced with an FDM 3D printer to be used as a marker of MRI and CT. Copper sulfate, used in the stereotactic frames for neuronavigation and seen as hyperintense on pre- and postcontrast T1-weighted MR images, was placed inside this object (Fig. 1C). This marker was fixed with double-sided tape to the skin on the forehead or vertex of the patient (according to the surgical position) after the inside of the frame had been outlined with a skin marker pen, and MRI was performed. Another same-sized hollow object was produced by the 3D printer (Fig. 1D); the CT contrast agent, iohexol,⁸ was placed inside the hollow part; and the CT examination was performed with the frame placed on hairless skin according to the surgical position. The marker was fixed to the forehead for frontal, temporal, or parietal tumors. For the prone position, the marker was attached to the vertex. The markers are disposable, and new markers were used for each patient.

Segmentation

Segmentation is the creation of anatomical structures, lesions, and other objects with 3D boundaries from 2D images (DICOM files in our study). This technique is

frequently used in medical image processing and in visualization of structures for 3D measurements (volume, surface, and shape properties), for producing 3D printable models, and in analytical spatial 3D surgical planning. While segmentation was done manually 10–15 years ago by selecting the contour and content of the image, it is now done semiautomatically or automatically with the advancements of technology. The 3D view of a single structure is called the segment. Each segment has some properties such as name, color, and content, and these properties can be changed. Segments can overlap spatially. Each segment can be expressed in different ways; it can be created in 2 dimensions with binary-marked mapping or can be expressed as a 3D closed surface with a surface mesh. When segments overlap, the segments can be made visible, called layering, whereby each layer contains separate segments.

The patients included in our study had the 3D-printed marker fixed on the forehead or vertex (according to the surgical position), and preoperative routine cranial CT and/or MRI was performed and the images stored as DICOM files via the Sectra IDS7 (version 20.2.9.3362; Sectra AB) workstation. With 3D Slicer (<https://www.slicer.org>), DICOM-formatted patient CT and/or MR images were imported and the threshold value was adjusted in Hounsfield units on CT with the 3D Slicer segment editor add-on. Tumor, bone, skin, and vascular structure segmentations were created with CT/MRI and/or CT/MRA in 0.5-mm- and 0.625-mm-thick sections, respectively. For MR segmentations, the threshold value was adjusted as intensity, and tumor boundaries were separated from the surrounding normal brain tissue by masking. This method can be used for segmenting objects that cannot be easily separated because they have similar image intensities and are very close to each other (Fig. 2).⁹ In these 3D images, the segmentations of the pathology were created with different textures, transparency, and color. Triangular-shaped marker segmentations containing CT or MRI contrast were segmented in a separate color for registration of the marker.

Fiducial Image Registration and Biomodel Positioning

The segmentations obtained from patient CT and MR images were matched with the 3D marker model by selecting 3 different points with the 3D Slicer (version 4.11; Slicer IGT, Fiducial Registration Module) program (Fig. 3),¹⁰ and their spatial coordinates were registered with other 3D segmentations (pathology, vascular, bone, and skin). All segmentations were transformed according to registration values by the 3D Slicer IGT module, and the 3D segmentations were saved with registered location data for the AR application development. With the help of this registration, the segmented 3D images in CT and MRI were matched with the AR marker.

App Development for Mobile Devices

Segmentations registered with the patient's forehead or vertex marker were processed using Unity (Unity Technologies) software. A camera-based object-tracking AR program was developed using the Vuforia Engine with a

FIG. 2. Bilateral contrast-enhancing T1 hyperintense, T2 hypointense occipital tumor, atrial myxoma metastases, adjacent to the superior sagittal sinus. **A:** Axial T2-weighted MR image of the tumor. **B:** Postcontrast axial T1-weighted MR image segmentation shown in green. **C:** Postcontrast coronal T1-weighted MR image segmentation shown in green. **D:** Postcontrast axial T1-weighted MR image showing a gadolinium-enhanced tumor in the bilateral occipital lobes. **E:** Postcontrast sagittal T1-weighted MR image segmentation shown in green. **F:** Three-dimensional segmentations made from MR images with 3D Slicer.

Unity and Vuforia developer account. The 3D registered segmentations of the patient were imported into the Unity program. The imported 3D segmentation location data, according to the AR marker, was preserved and coded. In this program, an interface was created for the intended platform (i.e., iOS 14.4, Android, Windows, or MacOS) and transferred to an iOS 14.4 mobile phone and tablet as a separate program for each patient with XCode (version 12.3; Apple Inc.).

Registration and Preoperative Preparation Time

The preoperative preparation time for segmentation and AR application development was collected separately for each patient. Registration of the AR application and the 3D marker placement interval was collected preoperatively for each patient. Registration failures and 3D segmentation shifts were recorded and statistically compared.

Perioperative and Intraoperative Use

The marker for the CT or MRI scan was removed from the frame and a 3D-printed marker for the AR application was placed instead on the patient's skin (forehead or vertex, according to the surgical position; previously tagged skin was visible and the edges of the frame fit with the skin tags) while the patient was under anesthesia. The app that was previously built and transferred to a mobile device was run, and the light detection and ranging (LIDAR) camera of the mobile device was used for precise AR neuronavigation. When running the app, the camera and target must be a short distance away (a minimum of 10 cm). Once the app detects the marker, 3D biomodels appear at

the same location where registration by 3D Slicer has been determined.

Accuracy Measurement

AR biomodels created with the mobile devices were compared with the Brainlab Kick optical tracking neuro-navigation system (OTNS) localization of the pathology at the medial, lateral, anterior, and posterior borders on the skin intraoperatively (Fig. 4). The difference between these borders is noted as the mean difference and calculated as the AR neuronavigation targeting error in millimeters.

Results

This technique was applied in 8 patients intraoperatively (Figs. 5 and 6). All patients had intracranial tumors: 4 frontal (50%), 2 temporal (25%), 1 occipital (12.5%), and 1 orbital (12.5%). The AR neuronavigation targeting error among the 4 borders of the real pathology ranged from 0.5 to 3.5 mm. The mean error was 1.56 mm with an SD of 0.79 mm and a median of 1.56 mm. The tumors were completely removed without any postoperative complications. The tumors were visualized preoperatively to determine the skin incision, craniotomy size, and location intraoperatively. In one case (patient 4), the OTNS had 5 mm of targeting error compared with the real localization of the tumor. Characteristics and histopathology of the tumors are shown in Tables 1 and 2.

The mean preoperative planning time of segmentation and application development was 35.7 ± 5.56 minutes. The median preoperative planning time was 37 minutes. AI-

FIG. 3. Registration of 3D segmentations with the 3D Slicer, Slicer IGT Module. **A:** Segmentation of CT or MR contrast marker and selection of 3 bottom edges of the biomodel. **B:** The 3D model of the designed AR marker and selection of 3 bottom edges of this model. **C:** Linear transform and registration of CT or MR marker segmentations. **D:** Registered view of AR marker, CT or MR marker, and tumor biomodels. **E:** Registered view of segmentations together with skin segmentation, superior view with the upper part of the skin removed to visualize the pathology. **FIG. 3. (continued)**→

FIG. 3. F: Registered view of segmentations, lateral view. CT or MR marker segmentation is *purple*; segmentation of the pathology is *green*; the designed AR marker at the same size and structure as the 3D-printed marker is *yellow*; and skin segmentation is *light yellow*.

though the preoperative planning time was longer compared with that of other neuronavigation systems, the preoperative registration time was 1.02 ± 0.3 minutes compared with 4 minutes, 25 seconds as previously reported for the preoperative registration time of other neuronavigation systems.¹¹

Discussion

With advances in modern medicine and technology, neurosurgery has become more precise, less invasive, and more complex. It is very difficult to meet the requirements for high sensitivity with traditional neurosurgical methods. Therefore, the concept of neuronavigation was first introduced in 1986. Neuronavigation systems provide the opportunity to show the exact location and structure of the target tissue in cranial and spinal surgery. These systems are widely used in modern neurosurgery, but they have some important shortcomings. First, they display 3D patient-specific images on a 2D screen and plane, which is an obstacle for the surgeon to understand the patient's anatomy. Another limitation is that these systems, which have a separate screen, draw the surgeon's attention out of the surgical field, increasing exhaustion, surgical time, and the potential risk of error due to the attention shifts to a different area. Another disadvantage is the long setup time in the operating room before surgery. All neuronavigation systems have targeting error; error up to 2 mm is acceptable by the US FDA for intraoperative use.

With the introduction of AR technologies in medicine, it has been possible to use these systems in the field of neuronavigation. In this method, a comprehensive view can be obtained by combining real and virtual objects. Patient-specific models, plans, and preoperative radiological images can be used for virtual imaging. With AR technology, the previously mentioned deficiencies of neuronavigation can be corrected. Distraction due to the surgeon looking at another screen can be prevented with this system. Although AR is newly established in neurosurgery, it is a clinically accepted innovation that has a wide range of medical uses.¹² Advantages of this technology are that the internal structures can be seen from the beginning of surgery and the surgeon is less distracted, and the virtual objects created play an active role in surgical planning and decision-making. It is thought that the use of AR in neurosurgery will open a new horizon in surgical planning and will play a major role in the future.¹³

Intracranial tumor surgery is the field with the most studies on AR navigation in neurosurgery. The importance of the pathways in the cerebral cortex and white matter makes it necessary to navigate this region with high acuity. Injury to neighboring eloquent structures can lead to postoperative neurological deficits. In this sense, AR neuronavigation may contribute to minimally invasive surgery without additional deficits by facilitating intraoperative planning and surgical guidance to the target pathology.

In the literature, AR neuronavigation studies are divided into 3 groups:¹³ point-to-point navigation, volumet-

ric navigation, and phone-based navigation. In our study, unlike previous studies, neuronavigation was applied by combining a 3D printer with AR technology in mobile devices (i.e., a phone or tablet) and marker assistance to create a fast, practical, and low-cost technique. In previous studies, AR neuronavigation systems were defined with a mean targeting error (root mean square) ranging from 0.75 to 4.61 mm compared with OTNSs or projection systems. In our study, this value was found to be 1.70 ± 1.02 mm with a median of 1.58 mm, and it was considered a usable method like those among earlier studies. Mobile devices with iOS or Android operating systems can be used, and no other equipment is necessary.

The preoperative preparation (segmentation, registration, and application development) time was calculated as 35.7 ± 5.56 minutes. Li et al. found a preoperative planning time of 40.2 minutes in the process of external ventricular drain placement using mixed reality.¹⁴ Incekara et al. used a neuronavigation system with mixed-reality glasses; they reported a preparation time of 5 minutes, 20 seconds, and it was shown that there was a positive learning curve.¹¹ In our study, it took less than 1 minute to run the app from a mobile device and place the marker. This time will be shorter on computers with higher processing power. The time frame, which was also shown to have a positive learning curve, tended to decrease gradually in our study when comparing the first patient and the last patient (39.1 minutes for the first half of patients and 31.8 minutes for the second half of patients, $p < 0.05$). The registration and intraoperative preparation time in our study was significantly shorter than with standard neuronavigation systems ($p < 0.05$).

OTNSs require patient head stabilization systems such as the Mayfield clamp. High projection errors have been reported for the infrared sensitive skin markers used for neuronavigation systems, and these systems are not easy to use due to a separate monitor and the frequent attention shift.¹⁵ At the same time, there are other limitations such as difficulty in face recognition and registration, and high targeting errors in prone-position surgeries. In our study, it was appropriate to use the AR neuronavigation system in the prone position and in other surgical positions without using head stabilization, including for pediatric patients, and no significant difference was found between surgery positions. For this reason, it is possible to use the system in patients who cannot be stabilized with a head clamp (e.g., pediatric patients and patients with skull base or convexity bone fractures).

Current surgical neuronavigation systems are high-priced tools. In a study of surgical neuronavigation systems, the neuronavigation market share was found to be \$372.7 million in Western Europe, \$110.9 million in Asia, and \$195 million in the United States in 2016.¹⁶ The cost of neuronavigation per procedure was reported as \$14,480,¹⁷ and it was stated that the cost of the neuronavigation system was between \$250,000 and \$950,000. In our study, the cost of a 3D-printed marker was almost negligible.

FIG. 4. Measurement of the accuracy of AR neuronavigation compared with OTNSs. Determination of anterior, posterior, lateral, and medial borders of a frontal parafalcine meningioma with AR neuronavigation and an OTNS. The differences between these measurements were assessed and compared statistically.

FIG. 5. Preoperative and intraoperative AR neuronavigation images (taken with an iPhone) with the patient in the prone position. **A:** Preoperative surgical planning with AR neuronavigation. **B:** Intraoperative use of the 3D-printed marker and AR application after craniotomy. **C:** Intraoperative AR images with brain segmentation.

Our AR neuronavigation technique has several limitations. It is marker-based neuronavigation; the marker is fixed on the skin (forehead or vertex) of patients at CT or MRI. The need of a marker complicates the installation of this system. For safety purposes, fixing the location of the marker was achieved by fixing the frame with dual-sided tape and skin tagging. The other limitation of this technique is the need for a mobile device. This AR neuronavigation system is not currently capable of detecting brain shift or deformation due to CSF leaks or surgical position, similar to OTNSs. Registration and correction of shift using intraoperative MRI and intraoperative ultrasound is the main solution of this targeting error, but these systems

are relatively impractical and high cost. Our AR technique can be further developed and easily integrated with these intraoperative imaging modalities. The battery life of mobile devices is another limitation; however, the app may be used on multiple devices. We always developed and transferred the application to both a mobile phone and a tablet in case one of them malfunctioned or ran out of battery. The battery life of both devices was long enough for use during the full operation time so that we did not have problems with battery life. With wearable head-mounted devices (Microsoft HoloLens and Magic Leap) and mixed-reality glasses, it is a great convenience that the surgeon does not have to look at another screen and can see AR

FIG. 6. Operating room setup. **Left:** Perioperative use of marker-based AR neuronavigation. **Right:** Intraoperative setup and use of the marker-based AR neuronavigation.

images in the direct field of view. However, this feature has some technical shortcomings. The first of these is high cost. Second, the angle of the camera is inconsistent with the surgeon, and incongruity can occur between the surgeon's hand and eye. Additionally, the screen reflected in these glasses is very small due to technical limitations, so the surgeon experiences fatigue while concentrating on the screen for a long time. Finally, another limitation is, again, low battery life.¹³

All neuronavigation systems have important practical concerns about error when using preoperative images. Intraoperative imaging increases the accuracy of neuronavigation systems by addressing the changing position of the lesion after dural opening, tumor resection, and cyst decompression on removal of CSF.⁶ Our AR neuronavigation system could be established with intraoperative imaging without any problem, but further studies must be performed.

There is a time synchronization problem in all AR and MR systems. Sudden change of perspective by the surgeon causes some time delay between the virtual and real image. In our study, this was not particularly noticeable. The frequency of creating and displaying AR images on the camera and screen was measured as 60 frames per second, and an average delay of 10 frames (0.2 seconds) was determined. The number of pixels in the camera sensors was measured as 12 megapixels and image resolution was measured as 1232 × 2688 pixels. With these values, image analysis and navigation can be done easily and precisely. In previous studies,¹⁸ a flickering sensation in the image was seen as very restrictive for navigation, but in our marker-based study using high-resolution image quality, image flickering was not noticeable to the eye and did not cause a disadvantage during the procedure.

Conclusions

In this study, we demonstrated that 3D-printed marker-based AR neuronavigation is an accurate, precise, and easy-to-use tool for neuronavigation. The proposed system is as precise as standard neuronavigation systems and more cost-effective. Three-dimensional segmented virtual images of targeted brain tumors corresponding to the surgical field were clearly visualized before and during surgery. This technique is preliminary for AR neuronavigation and its routine use in neurosurgery. The intraoperative capabilities of this system, the combination of 3D printing and AR technology, and the clinician-facilitated development has potential for routine use and can play an important role in neurosurgical planning, neuronavigation, and greater understanding of the 3D anatomy of the pathology. Our technique has the ability to show accurate location of the pathology in all surgical positions, especially the prone position—and under different conditions, such as awake craniotomies and minimally invasive surgeries—compared with the high targeting error with prone positions in traditional neuronavigation systems. This AR neuronavigation is promising for use intraoperatively with high accuracy and low cost, but more experience and further studies with more patients are needed to establish the efficacy of its use alone as the main neuronavigation system.

This technique can potentially be applied to other regions of the body and other pathologies. With further development, our AR neuronavigation technique may have wider clinical use such as with vascular surgery, hydrocephalus shunt surgery, external ventricular drain placement, and spinal surgery. As a continuation of this study, we intend to visualize the tumor in real time with mixed-reality head-mounted devices during tumor excision.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Yavas. Acquisition of data: Yavas, Caliskan. Analysis and interpretation of data: Yavas. Drafting the article: Yavas, Caliskan. Critically revising the article: Caliskan, Cagli. Reviewed submitted version of manuscript: Cagli. Statistical analysis: Yavas, Caliskan. Administrative/technical/material support: Caliskan, Cagli. Study supervision: Cagli.

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