



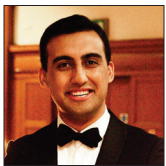
Technical Notes

Early experience with patient-specific low-cost 3D-printed polymethylmethacrylate cranioplasty implants in a lower-middle-income-country: Technical note and economic analysis

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ABSTRACT

Background: Polymethyl methacrylate (PMMA) cranioplasty, while widely prevalent, has limitations associated with freehand manual intraoperative molding. PMMA has been superseded by titanium or Polyetheretherketone implants, prefabricated commercially from preoperative CT scans, and boasting superior clinical and cosmetic outcomes. However, such services are extremely inaccessible and unaffordable in the lower-middle-income country (LMIC) settings. The study aims to describe, in detail, the process of making ultra-low-cost patient-specific PMMA cranioplasty implants with minimum resources using open-access software. We report the first such service from the public health-care system within Pakistan, a LMIC.

Methods: Using open-source software, preoperative CT heads were used to prefabricate three-dimensional implants. Both implant and cranial defects were printed using polylactic acid (PLA) to assess the implant's size and fit preoperatively. From the PLA implant, we fashioned a silicon mold that shapes the PMMA implant. Ten patients who underwent cranioplasty using our technique for various cranial defects with at least a 12-month follow-up were retrospectively reviewed. Clinical, cosmetic, and radiological outcomes were objectively assessed.

Results: Etiology of injury was trauma (8), malignant MCA infarct (1), and arteriovenous fistula (1). We produced seven frontotemporal-parietal implants, one bifrontal, one frontal, and one frontoparietal. At 1 year, eight patients reported their cosmetic appearance comparable to before the defect. Radiological outcome was classified as "excellent" for eight patients. No postoperative complications were encountered, nor did any implant have to be removed. One patient's implant involving the orbital ridge had an unsatisfactory cosmetic outcome and required revision surgery. The average cost per implant to the National Health Service was US\$40.

Conclusion: Prefabricated patient-specific PMMA cranioplasty implants are cost-effective. A single surgeon can fashion them in a limited resource setting and provide personalized medicine with excellent clinical/cosmetic-radiological results. Our method produces patient-specific cranioplasty implants in an otherwise unaffordable LMIC setting.

Keywords: 3D Printing, Cranioplasty, Low cost, Lower middle income country, PMMA polymethylmethacrylate, Silicon mould

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INTRODUCTION

Polymethyl-methacrylate (PMMA) is one of the most prevalently used allogenic materials for cranioplasty. It is low cost, radiolucent, nonconductive, nonirritating, lightweight yet strong, inert, and nonferromagnetic.^[2,7,19] PMMA was superseded by patient-specific 3D-printed titanium or Polyetheretherketone (PEEK) implants, which, while having their own complication profile and limitations, have been accepted to have far superior outcomes compared to freehand intraoperative PMMA castings, especially in large-sized defects.^[1,10,12,14]

Pakistan is a lower-middle-income country (LMIC) with a population of over 220 million. Neurosurgery is accessed by the masses, who are the socioeconomically poor and underprivileged, in National Health Services (NHS) government-funded hospitals and is free of cost. The NHS, however, does not cover the bill for PEEK or Titanium 3D-printed implants, and to date, freehand PMMA has been the cranioplasty of choice due to economic limitations.

While the emergence of 3D printers and specific computer software allowed the printing of implants, both PEEK/titanium as a material and 3D printers which can print from them are not affordable to LMIC hospitals.^[4,8,21] Open-source 3D technology with desktop computers and personal 3D printers allowed neurosurgeons to produce in-office patient-tailored implants at low costs.^[17] The objective of this paper is to provide a technical description and experience of the first patient-specific 3D-printed cranioplasty service in the public health care system of Pakistan. These PMMA based implants are ultra low cost to manufacture and hence feasible for public healthcare systems of LMICs to provide. We discuss our workflow, and the cost effectiveness of such implants in the context of our LMIC setting.

MATERIALS AND METHODS

Patient population and operative parameters

We retrospectively reviewed patients, in whom a patient-specific cranioplasty prosthesis was implanted, designed using open-access software, and printed using our 3D printer. Institutional ethics approval had been sought before the study, and individual patient informed consent was obtained to use photographs. Preoperative data included sex and age, etiology of injury, CT scan-based implant area to be modeled, and the time between initial operation and cranioplasty. We reviewed the intraoperative surgical technique, location, and need for drain placement or revision. Postoperative data were reviewed for complications such as infection, hematoma, hydrocephalus, implant rejection, seizures, cosmetic outcome, and financial aspects of the modeling and operation. We report each resource utilized for this service, its price, and the time taken for each step in the procedure.

Printing procedure and cranioplasty

Acquisition of CT data

CT scanning (including 3D reconstruction) is free of cost to patients at our institution and public sector hospitals if they are admitted as inpatient care. When advised in an outpatient setting, the cost is 1000 PKR (US\$5) and, therefore, is still heavily subsidized by the government. For comparison's sake, the same scan would approximately cost 15,000 PKR (US\$75) if done at a private commercial laboratory. In this series, no patient had to pay for their CT scan. High-resolution 1 mm CT data contiguous to the head of patients who underwent a craniectomy were obtained using a volumetric 32-slice Phillips CT scanner and transported to a Windows desktop computer as 3D volumetric DICOM data files.

DICOM conversion to stereolithography (STL) format

We used 3D Slicer, a free open-source software package used for medical, biomedical, and related imaging research, to convert DICOM CT data to STL of the skull. In Segment Editor of 3D Slicer, the "Threshold" effect was used to segment bone out of the brain and soft tissues with at least 250 lower threshold values. The newly created segmentation was exported in STL format.

Cranial plate designing

We used the free software Autodesk Meshmixer to design our cranial plate for the skull defect. STL file designed from the previous step was imported in Meshmixer; using "Analysis" from toolbar "Inspector" repairs the meshes and errors in the STL file.

Using the "Select" toolbar, the outer boundary of the defect was selected, while "symmetry" was checked. This created a mirror selection boundary on the opposite half of the skull. After disabling the "symmetry" option on the opposite side, the entire area within the boundary was selected. From the "select" menu, we click "modify," and then, "smooth boundary" option is used. Then from the "edit" option, "separate" is selected. The "mirror" option mirrors the selected area on the opposite side. A 3–5 mm thickness is added to the mirrored surface using "extrude" tool. To prevent a tight-fitting between prosthesis and skull, an offset of 1 mm is added to the original skull, and then, the "Boolean Difference" function is used to create the prosthesis. The designed prosthesis is exported as an STL file.

Printing of cranial plate using PLA

STL files of both the skull model (with defect) and the prosthesis were "sliced" with computer software (Ultimaker Cura) with the following settings: infill: 30%; shells: 2;

layer height: 0.2–0.4 mm; extrusion temperature: 210°C; bed temperature: 50°C; and the additional supports. Slicer files were transferred to the open-source Prusa i3 clone 3D printer assembled locally (\$US 280–300). It takes roughly 4 h to print a frontal-parietal implant and anywhere between 4 and 8 h for a frontal-temporal-parietal implant. All software used is easily available and compatible with Windows OS. The skull defect and cranioplasty implant are printed using polylactic acid (PLA). Printing the skull defect helps us check the proper fitting of the implant preoperatively.

Silicon mold preparation

Silicon rubber was mixed in two parts, a base and a catalyst, to induce curing. We used food-grade silicon from Chinese manufacturers. For mold preparation, we made a two-part silicone mold. The silicon base was mixed in a ratio of 100:1 with catalyst as recommended by the manufacturer. A silicon layer is poured into an appropriate-sized plastic lunchbox/container, and then, the PLA 3D printed prosthesis is added. When this layer was cured (cure time was 6–8 h), a thin layer of the plastic sheet was placed over it to prevent adhesion with the opposite part of the mold, and the second layer of silicon was placed above it. After curing, the two parts were separated, and the PLA prosthesis was taken out. The silicon mold adapts the impression of the cranioplasty plate incorporating the inner table (drag) and outer table (cope), forming a negative mold.

Forming PMMA cast

The PMMA resin of slow viscosity was then poured into the prefabricated mold to acquire the shape of the cranioplasty plate being modeled. After 7–10 min, the PMMA cranioplasty implant was removed and cooled in normal saline when

the exothermic reaction began. After setting/hardening the PMMA prosthesis, the fit was checked by placing the implant on a skull model with the defect of the same patient printed with our 3D printer. Sometimes minor cutting or grinding may be needed, but most of the time, the fitting was perfect.

Sterilization and surgery

The PMMA implant was washed with 0.9% saline to remove any debris. It is then wrapped in sterilization wraps and placed in a Pre-Vacuum sterilizer for 30 min at 121°C at a pressure of 1.0 bar. The prosthesis was implanted in a standard cranioplasty fashion, where all patients received preoperative antibiotics and a postoperative CT scan within 24 h. Our entire process is illustrated and summarized in Figures 1-3.

Clinical cosmetic outcome measurement

The operating surgeon did a clinical evaluation with a minimum follow-up of a 12-month clinic visit. The patient reported their satisfaction on a self-reported 10-point scale, where 10 indicated appearance comparable to how they looked before the defect. In addition, a 5-point ordinal scale was utilized as employed in the previous literature, where the patient was asked to rate their overall outcome on a scale of 1–5, where one is very dissatisfied, two is somewhat dissatisfied, three is neutral, four is somewhat satisfied, and five is very satisfied.^[17]

Radiological outcome assessment

Assessed postoperatively and at follow-up by CT scan.^[23]

1. Excellent: implant correctly aligned within 1 mm of the defect

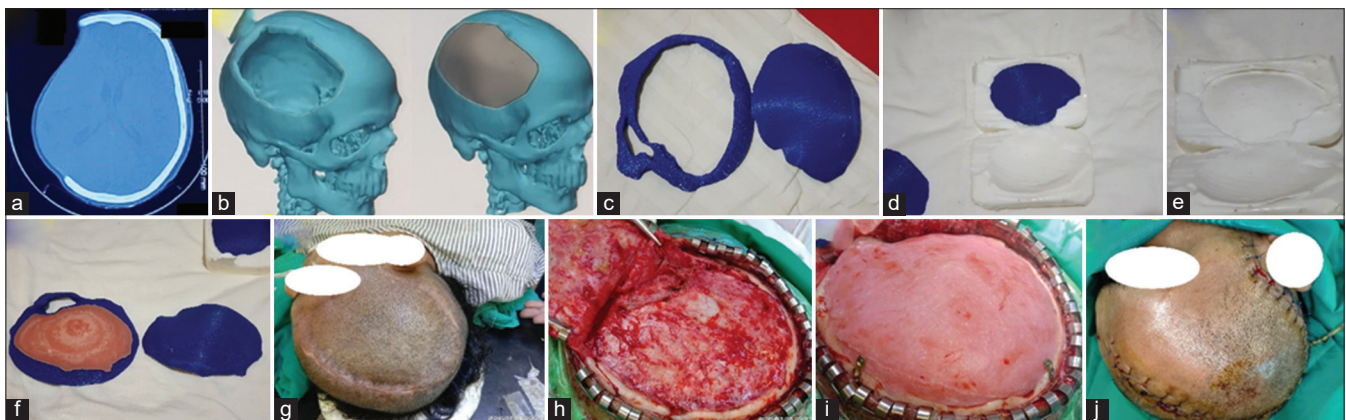


Figure 1: Illustrating workflow (a) preoperative CT scan, (b) modeling cranioplasty implant for printing using reference curves or Boolean subtraction, (c) 3D print of skull defect and cranioplasty implant with polylactic acid (PLA) to assess fit, accuracy and shave if needed, (d and e) creation of silicon resin mold from PLA cranioplasty implant, (f) PMMA implant created from silicon mold fitted in defect model (g and h) preoperative picture, (i) PMMA implant fit and fastened with titanium screws, and (j) postoperative picture.

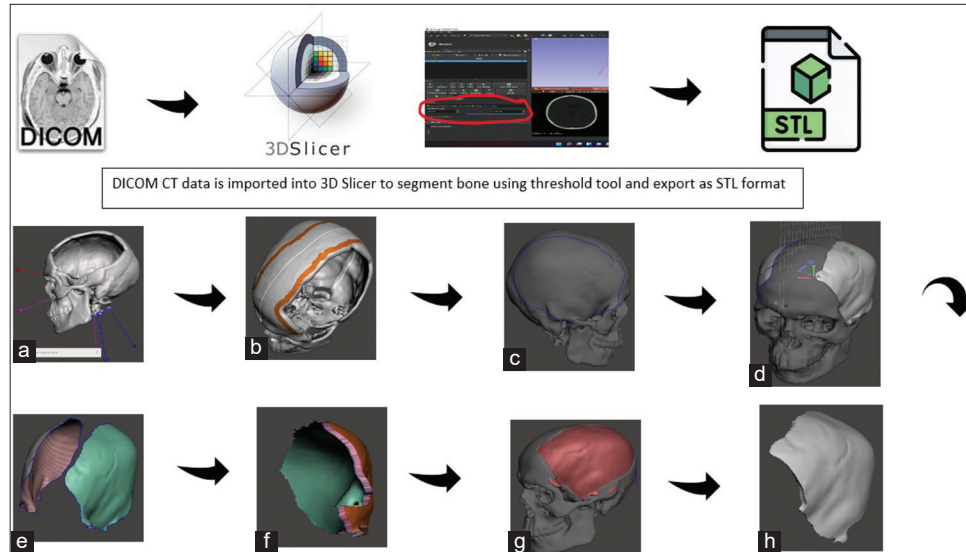


Figure 2: Illustrates the workflow for the design process of the prosthesis and skull model (with defect) to be printed. STL is imported in Meshmixer, Inspector tool remove errors (a), defect outline is selected using symmetry option outlining to opposite skull (b), Opposite side of skull selection is separated from skull (c), Separated surface is mirrored (d,e), Thickness is added to mirrored surface (f), Offset added to skull of about 1mm and then cranial plate is created by Boolean difference tool (g, h).



Figure 3: Illustrates patients' preoperative picture who had previously undergone a large frontal-temporal-parietal decompressive craniectomy (a), and the postoperative picture with patient-specific PMMA cranioplasty implant (b). Images attached after being reviewed by the patient to provide informed consent. Patient reported cosmetic outcome = 10, satisfaction = very satisfied, radiological accuracy = excellent.

2. Accurate: implant dislocated but equal to surrounding skull thickness
3. Inaccurate: any area of implant dislocated and greater than surrounding skull thickness.

RESULTS

Table 1 summarizes and Figure 4 illustrates our patients' baseline characteristics. The mean age of patients was 36.6 years, ranging from 24 to 60 years. There were 8 (80%)

males and 2 (20%) females in this cohort. Indication for craniectomy was mostly trauma ($n=8$, 80%), followed by a spontaneous subdural hematoma as a result of frontal arteriovenous fistula ($n = 1$, 10%) and a malignant middle cerebral artery infarct ($n = 1$, 10%). Of the eight patients with trauma etiology, seven underwent a unilateral decompressive frontal-temporal-parietal hemicraniectomy.

The median time between previous surgery and cranioplasty was 7 months. The average fronto-temporal-parietal defect size was $12.88 \text{ cm} \times 11.39 \text{ cm}$ (craniocaudal*anterior-posterior). There were no infections, wound dehiscence, or implant rejection in the immediate postoperative period, nor did any implants need to be removed. All patients had a 12-month follow-up except patient 5. At 12-months, clinical evaluation by the surgeon was reported as excellent with no visible defect and good results overall across all cases except patient 5, where there was a visible gap between the implant and orbital region. A reoperation for patient 5 is still pending. The cosmetic appearance of all patients had profoundly improved. Out of ten patients, 8 (80%) reported ten out of ten cosmetic score; while 2 (20%) patients reported seven and eight out of ten. The former eight patients on the 5-point scale reported their satisfaction as five (very satisfied), while the latter two patients reported a score of four (somewhat satisfied). Patient number 2, who reported a cosmetic score of eight out of ten, reported minor discomfort, as they could feel a gap between the bone flap and the implant site. This was a 1 mm gap at the supraorbital region, but no revision was performed as the gap was not visible, and the patient did not want a second surgery. For patient 5 [Table 1], cosmetically, the orbital ridge was protuberant, as shown in Figures 4 (numbers 3 and 5) and 5.

Table 1: Patient demographic, baseline characteristics, and cosmetic, clinical, and radiological outcomes for each patient.

Patient Number	Age/Sex	Mechanism of Injury	Injury Morphology/ Aetiology	Cranial Plate	Size of Defect/ Implant in Centimetres (Cranio-Caudal* Anterior-Posterior)	Time Between First Surgery and Cranioplasty in Months	Cosmetic Score	Radiological Accuracy
1	35/F	Trauma	ASDH	FTP flap	13.5*10.8	7	10/10	Excellent
2	45/M	Trauma	ASDH	FTP flap	11.2*12.6	7	8/10	Accurate
3	34/M	Trauma	ASDH	FTP flap	12.3*11.8	7	10/10	Excellent
4	60/M	Malignant MCA Infarct	MCA Aneurysm	FTP flap	9.9*12.3	8	10/10	Excellent
5	28/M	Trauma	Frontal Contusion	Frontal	6.2*6.1	7	7/10	Inaccurate
6	30/M	Trauma	Bifrontal Contusion	Bifrontal (2 flaps)	8.8*10.6 and 12.1*10.7	7	10/10	Excellent
7	27/M	Spontaneous Subdural Hematoma	Frontal AV Fistula	FP flap	7.6*6.5	9	10/10	Excellent
8	45/F	Trauma	ASDH+Frontal Contusion	FTP flap	16.5*10.4	7	10/10	Excellent
9	24/M	Trauma	ASDH	FTP flap	13.3*11.05	8	10/10	Excellent
10	38/M	Trauma	ASDH+Frontal Contusion	FTP flap	13.5*10.8	7	10/10	Excellent

Age is given in years. F: female, M: Male, ASDH: Acute subdural hematoma, MCA: Middle Cerebral Artery, AV: Arteriovenous, FTP: Fronto-temporo-parietal, FP: Fronto-parietal.

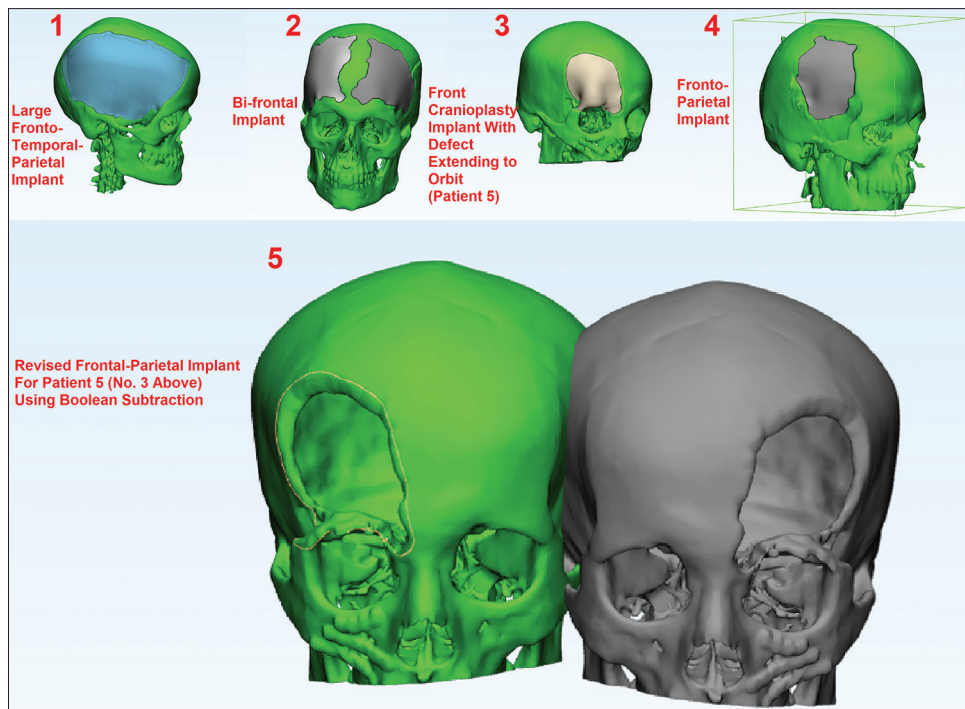


Figure 4: Illustrates implant model generation for select cases. Numbers 3 and 5 show the original and revised implant, respectively, for patient 5 [Table 1].

Finally, Table 2 shows the individual components required and their standard price to generate at any local market. This approximates to be roughly 6600 PKR (US\$40) per patient. The operating surgeon purchased these consumable materials from local commercial shops.

DISCUSSION

PEEK or titanium 3D printers can cost from US\$37,000 to US\$310,000, and prefabricated implants can cost up to US\$10,000.^[3,5,6,9,11,15,16,18,20-22] Price is perhaps the most important consideration in an LMIC setting such as ours, where median monthly income is approximately US\$500. PMMA is an attractive option given the minimum price. Still, as a material and technique, freehand PMMA sculpting has generally had inferior outcomes, including a higher prevalence of wound healing disorders, higher rates of early re-operative revisions, a higher prevalence of extradural hematoma, cerebrospinal fluid leak, poor radiological accuracy, and inferior cosmetic results compared to implants modeled using preoperative CT scan-based 3D printing.^[1,10,12,14] We demonstrate that with a personal minimum specification 3D printer and open-source software, it is possible to benefit from PMMA's affordability while improving its cosmetic accuracy, and have minimum complications. The software learning curve is minimum, and a single neurosurgeon began the service with no formal training in computer science or information/technology. We had no adverse events from

the procedure except one patient's implant being printed inaccurately due to technical inaccuracy in the design process (patient 5). For patient 5, while the posterior aspect of the implant was accurate, anteriorly, its gap with the orbit was wider than expected [Figure 5].

Different neurosurgeons, in their own settings, have utilized technology for patient benefit by producing low-cost implants. Yerragunta *et al.*^[23] use acrylonitrile butadiene styrene (ABS) plastic for printing a negative impression mold. ABS is not specifically made for 3D printers, but rather an injection molding is difficult to print and may shrink. We use PLA as it is easily printable, environmentally safer, and biodegradable. Kim *et al.*^[13] and Morales-Gomez *et al.*^[17] use a two-part mold, whereas our silicon mold was one part, analogous to an open book [Figure 2d and e], where silicon was dissected from the middle with a knife to create a flap allowing us to pour PMMA. We feel that this is easier and does not compromise accuracy. In addition, we print the defect using PLA and thus assess the accuracy of the PMMA implant fit without intraoperative pressure. In addition, the studies cited above do not provide a detailed breakdown of the costs of each component or the time taken by each step; therefore, a direct comparison is difficult. Our components and their price are summarized in Table 2. Yerragunta *et al.*,^[23] total price for a single frontal-temporal-parietal implant is US\$307, but they do not state the price or spec of their printer. Kim *et al.*^[13] make no mention other than citing US\$450 being the approximate cost for producing the prefabricated molds in their series. Morales-Gomez *et al.*^[17] only report the total price of an implant ranging from US\$135 to US\$444 (mean US\$308), their printer was approximately US\$2,500 to US\$3,500, which may not be affordable in every setting.

Table 2 : The materials required for making a custom cranioplasty implant. The rates quoted are from local commercial markets and were purchased out of pocket by the surgeon, who was later reimbursed. CT scan prices at government-funded hospitals are heavily subsidized and free if required inpatient. The prices quoted for private laboratories are the current approximate price at the time of writing.

Our study component	Price
Polymethylmethacrylate bone cement	4000 PKR (\$US25)
Silicon resin	2000 PKR (\$US12)
Polylactic acid	150–300 PKR (\$US1-3)
Total Price	Approximately \$US40
3D printer (locally assembled non branded)	40,000–45,000 PKR (\$US280-300)
Extras For Context	
CT scan for an inpatient (including 3D reconstruction)	Free of Charge
CT scan for an outpatient (including 3D reconstruction)	1000PKR (US\$5)
CT scan from a private laboratory (including 3D reconstruction)	15,000 PKR (US\$75)



Figure 5: Patient number 5 [Table 1] whose implant was inaccurate both radiologically and poor cosmetically. Image attached after being reviewed by the patient to provide informed consent. Patient-reported cosmetic appearance = 7, satisfaction = somewhat satisfied, radiological accuracy = inaccurate.

A logistical limitation to our 3D printer is the lack of automatic detection of thread breakage and stopping of print. This meant one would have to “babysit” the printer and occasionally check for breaks which required a full-time presence during a long printing process, although this had never occurred. This may be a feature in better 3D printers in the same overall price range.

Designing and printing the implant for a single patient would take an entire day, especially as the printer must be monitored. Issues may arise with the loss of electricity at home. We are now beginning to train our residents in the design process and have purchased a printer for our department. This addresses the issues of electricity load shedding in personal residences affecting printouts and the surgeon’s electricity bill and reduces the burden on a single consultant for the design process. With one of the lowest reported prices in the literature (US\$40) for a patient-specific frontal-temporal-parietal cranioplasty implant, the bill for expendables is covered by our NHS or through the Zakat (National Islamic Charitable) fund without costing the patient anything.

One advantage of our study is that we defined and assessed radiological accuracy, unlike other studies,^[13,17] and our cosmetic outcome assessment parameters are clearly defined. We add to the literature describing our technique, in the context of an LMIC setting, of producing patient-specific PMMA implants using open-source resources. Such methods are beneficial to public healthcare systems in both the developing and developed world. We are fortunate to transfer the knowledge/skill of this technique to our colleagues at the Punjab Institute of Neuroscience in Lahore. With a high volume of trauma at our centers, we hope that with ongoing prospective collaboration, the major limitation of this report, that is, the small sample size, will be improved on and the necessary numbers and follow up duration will be obtained to provide a more substantial assessment of the outcomes that such implants may provide, and the benefit derived to public health care systems/their cost effectiveness.

It is important to acknowledge that the median cranioplasty time is moderately longer than what we aim for at our unit, which is usually 4 months. This is because the cases discussed in this technical note underwent a craniectomy in the last month of 2019 and the first few months of 2020. Then from March 2020 onward, significant disruptions occurred in clinical service due to the initial waves of the global COVID-19 pandemic, including complete and episodic cessation of elective casework, including cranioplasty and our neurosurgical ward and staff deployed as part of the COVID response. Most “cold” elective cases have still not returned to normal volume. In addition, the pandemic not only affected the provision of clinical services but also contributed to patient follow-up delays.

It is the responsibility of the neurosurgeon, particularly in the developing world but also in affluent economies, to

integrate technological avenues to drive their field forward in achieving the tenants of global neurosurgery, which includes empowering health equity and accessibility of high-quality neurosurgery to everyone, thereby increasing health outcomes and quality of life for all.

CONCLUSION

We demonstrate the technical procedure of producing low-cost patient-specific PMMA cranioplasty with a local desktop and 3D printer designed by a single neurosurgeon with the potential to provide clinical, cosmetic, and radiological outcomes and is the most beneficial and feasible economically for public healthcare systems and LMIC patient populations. Further, detailed long-term prospective studies with larger sample size and follow-ups are required to establish such techniques clinically and demonstrate their benefit to public health-care systems.

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Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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