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A retrospective evaluation of 192 implants placed in augmented bone: a six-year mean follow-up study.

--Manuscript Draft--

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Abstract:	The purpose of the present study was to assess the cumulative survival rate (CSR) of 192 implants placed in association with guided bone regeneration (GBR) procedures to evaluate the long-term predictability of this technique. Moreover, the Kaplan Meier survival analysis was applied to the data in order to evaluate predictors of implant failures including the source of the graft, the type of membrane and the timing of implant placement.. The CSR of the sample was 96% ± 2% over about a "6-year" mean follow-up period. Considering the source of graft, a 95%, 93% and 98% CSR was obtained for DBBM, autologous, and 1:1 ratio mixture of autologous and DBBM grafts. The CSR referred to bioabsorbable membranes was 96%, whereas 95% was the CSR reported for non-resorbable membranes. The CSR of simultaneous surgeries was 97% whereas staged surgeries showed a CSR of 95%. According to the data, implants placed in conjunction with GBR procedures presented a satisfying survival rate even in the long-term period. All the procedures performed with different bone grafts and type of membranes guaranteed optimal results both in one- and two-stage approaches. No statistically significant differences could be detected among the groups; indeed the use of DBBM associated with resorbable membranes may be suggested to reduce patients' morbidity and treatment time. Therefore, the dental implants placed in association with bone regenerative procedures presented safe and predictable long-term clinical results.
Response to Reviewers:	Department of Dental Implants, Maxillo-Facial Surgery and Odontostomatology Unit. Fondazione Cà Granda IRCCS, Ospedale Maggiore Policlinico. Milan, Italy.

Milan, December 28, 2014

Journal of Oral Implantology
Editor-in-chief

Response letter to: Journal of Oral Implantology.
Title: RETROSPECTIVE SUCCESS ON 192 IMPLANTS PLACED INTO REGENERATED BONE WITH GBR TECHNIQUE: A SIX YEARS SURVIVAL RATE MEAN FOLLOW-UP

Dear Editor and Reviewer,
enclosed You will find the responses to the Reviewer's comments. Firstly, let us open by thanking the Reviewer for their insightful comments. He gave us clear guidance and positive critiques. In the following lines we have detailed the changes in line with the Reviewer's comments.

Comments to Author:
Reviewer #3: Dear Author(s),
the quality of the manuscript has significantly improved in this resubmission.
There are still some points of concern that need to be addressed.

Major concern
Throughout the results section you are referring to follow-up time as being a 95% confidence interval. This is completely wrong. The confidence interval is a range within which the true survival rate of your statistic should fall into (with 95% confidence). The follow-up time that you are noting in the parenthesis is a totally different thing.
One example out of many:
"According to the Kaplan-Meier estimator, the cumulative survival rate (CSR) was 96% ± 2% (95% CI: 165,8 to 174,3 months)"
Please have a professional biostatistician verify the integrity of the statistical analysis reported in this paper.
Dear Reviewer accordingly with Your precious note, the paper has been modified by a professional statistician. He changed all the values and modified the text of the paper accordingly.
Thank You for Your support and for giving us the possibility of improving the manuscript quality

Minor comments
Title:
Do Journal guidelines recommend capitalization?
Also please reword for clarity. "Retrospective success" is not an appropriate term. This is a restrospective study evaluating implant success. Also not "on" 192 implants.
Consider this title or a title similar to this: " A retrospective evaluation of 192 implants placed in augmented bone: a six-year mean follow-up study"
Thank You for Your kind suggestion. We just changed the title accordingly with Your precious note

Abstract:
"discriminated". Please rephrase. Thank You I just replaced the sentence.
" Log rank test was used for assessing the statistical significance".This is vague. As i mentioned during the first revision log-rank tests refer to pairwise comparisons. Either elaborate on this or exclude this sentence from the abstract.
Yes I totally agree with You. Just removed that. Sorry for the mistake.
-You state that data were monitored for a mean 6 year follow-up. This may be deceptive. Please also state the range of follow-up in parenthesis.
-Thank You I just modified the sentence accordingly with Your precious suggestion.
-The last sentence is not conclusions. I agree with You, I just added a conclusion sentence. Thank You.

Introduction:
l26-l32 "Guided tissue regeneration...to...epithelial cell occlusivity". These sentences are very long and do not contribute anything to the introduction. I recommend removing them.

Thank You I just removed that.

Methods: l107 "Log rank test was used to assess the statistical significance."
Please see my comment above. Please try to be more precise. I recommend rephrasing to "Long rank tests were utilized to compare the survival rate for implants in each of the subgroups".
Yes, Thank You, I just used Your suggested one.

Result
As mentioned above all CIs are wrong. Please address very meticulously.
Also, report the overall follow-up time (and range).
Dear Reviewer accordingly with Your precious note, the paper has been modified by a professional statistician. He changed all the values and modified the text of the paper accordingly.
Thank You for Your support and for giving us the possibility of improving the manuscript quality

Conclusions:
"According to recent literature studies, GBR could be considered a predictable technique when
associated to alveolar ridge reconstruction for implant placement purposes." This cannot be part of the conclusions of your study. Readers are interested in the translation of your results. This is not a review paper.
I agree with You just deleted that sentence
Also please change "deepen" with "widen" or another appropriate term.
I did thank You

reference 2: Is this really relevant to your work? Dear reviewer, maybe that reference can be considered not so important, but we consider that relevant because during the introduction we want to underline some paper in which the regenerative procedure has been used. That reference is from 1988 and it is one of the first paper talking about the healing of bone regenerative procedure. I hope for Your kind understanding.
reference 6: "et al." is not the appropriate reference style. Ok Just modified that adding the other authors also in reference 34

Fig 1: Rx? Just replaced it with “radiographic”
Figure 8: "recovery" is not the appropriate scientific term. Thank You I just modified that.

We have made changes throughout the paper that address the points You have made. We hope that through our revisions we have strengthened the positive outcomes of our treatment protocol.
Thank you again for taking the time to share Your constructive feedback. I remain at Your disposal for further communications.

Sincerely,

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A retrospective evaluation of 192 implants placed in augmented bone: long-term follow-up study.

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Abstract.

The purpose of the present study was to assess the cumulative survival rate (CSR) of 192 implants placed in association with guided bone regeneration (GBR) procedures to evaluate the long-term predictability of this technique. Moreover, the Kaplan Meier survival analysis was applied to the data in order to evaluate predictors of implant failures including the source of the graft, the type of membrane and the timing of implant placement. The CSR of the sample was 95,6% over a mean follow-up period of 78 months (range, 1-175 months). Considering the source of graft, a 95,0%, 93,3% and 97,7% CSR was obtained for DBBM, autologous, and 1:1 ratio mixture of autologous and DBBM grafts. The CSR referred to bioabsorbable membranes was 96,5%, whereas 94,6% was the CSR reported for non-resorbable membranes. The CSR of simultaneous surgeries was 96,8% whereas staged surgeries showed a CSR of 94,5%. According to the data, implants placed in conjunction with GBR procedures presented a satisfying survival rate even in the long-term period. All the procedures performed with different bone grafts and type of membranes guaranteed optimal results both in one- and two-stage approaches. No statistically significant differences could be detected among the groups; indeed the use of DBBM associated with resorbable membranes may be suggested to reduce patients' morbidity and treatment time. Therefore, the dental implants placed in association with bone regenerative procedures presented safe and predictable long-term clinical results.

Keywords: Implants survival rate, Guided bone regeneration, Bone grafts, Barrier membranes, Dental implants.

Introduction.

Alveolar ridge resorption following tooth loss may hamper an ideal prosthetic driven implant placement. Additional bone augmentation procedures become mandatory in order to obtain adequate quality and quantity of hard and soft tissues for implant placement purposes [1,2]. The creation of a secluded anatomical site could not be considered the only prerogative of barrier devices, particularly when guided bone regeneration (GBR) is performed. Thus, in addition to epithelial cells occlusivity, GBR exploits space maintenance and graft containment properties to promote newly bone formation underneath the membrane [3]. The present concept has been recently emphasized by the fact that, despite occlusive barriers have reported impressive outcomes, even porous membranes could lead to predictable bone regeneration with results equal or superior to those of occlusive membranes [4-7]. Particularly, macroporous titanium mesh allows proper blood supply to the graft and facilitates a greater bone regeneration compared with microporous membranes, contextually preventing significant soft tissue ingrowth [8]. A direct comparison between horizontal and vertical augmentation in terms of clinical outcome is difficult to perform due to heterogeneity of data among the different studies, however both techniques have demonstrated predictable results with comparable implant survival rates [1, 9, 10]. Briefly, Jensen et al. found a 100% median survival rate of implants placed in both horizontal and vertical dimensions similarly to those reported for pristine bone [10]. In a recent systematic review concurring with the previously mentioned study, both horizontal and vertical GBR have proven to be effective, exhibiting comparable implant survival rates [1]. Purposes of GBR shift from increasing the availability of bone for a proper implant placement to reconstruct hard and soft tissues similar to the pre-pathologic condition. Different protocols could be applied to GBR depending on the source of graft, the type of membrane and the implant placement timing.

Although autogenous bone represents the gold standard for ridge augmentation procedures due to osteogenic and osteoinductive properties, drawbacks including donor-site morbidity, limited availability and possible complications related to the harvesting procedure as neurosensory disturbances, prolonged healing and opportunistic infections are reported [10, 11]. Limitations associated with the use of autografts have directed attention toward the use of bone substitutes [12]. So far, xenogenous bone alone or combined with autologous bone, used in combination either with resorbable or non-resorbable membranes during GBR procedures has shown encouraging results [12-15]. Several barrier devices have been developed to provide various functions in different clinical settings. The selection of a specific membrane is mainly dependent on biological and physical properties, which influence its function in relation to the anatomy of the bone defect and the required treatment, with each material bearing inherent advantages and disadvantages [5, 16]. Concerning GBR procedures, both bioabsorbable and non-resorbable membranes have demonstrated predictable results in terms of implant survival rate [13, 17], however this type of surgery appears to be highly technique-sensitive, therefore the applicability to a wider array of operators and clinical settings remains still unclear [18]. Lastly, the choice between simultaneous or delayed placement timing is mainly dictated by the residual bone amount. Indeed, the final goal of alveolar ridge reconstruction is the ideal implant insertion in a prosthetically driven position. If the native bone is sufficient to simultaneous implant placement, the observed advantages are mainly the reduction of the treatment time and besides, implant function as “tent screws” for the membrane in vertical regeneration. No clear evidence that the simultaneous or delayed implant placement may affect the implant survival rate in GBR procedures could be found in literature, however data concerning this aspect are still lacking [19].

The aim of the present study was to assess the survival rate of dental implants placed in augmented bone to evaluate the predictability of GBR procedures in the long-term period. Moreover, a retrospective analysis was conducted to evaluate the influence of possible predictors of implant failure including the source of bone grafts, the type of membranes and the implant placement timing on the implants survival rate.

Materials and methods.

Study design

In the present retrospective cohort study, 61 patients with a range age of 25 to 79 years treated from 1999 to 2012 in the same clinical center (Department of Implantology, U.O.C. Maxillofacial Surgery and Odontostomatology Unit, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy) were analyzed. The examiner was a postgraduate doctor in dental surgery (DDS) belonging to the above-mentioned Department, who evaluated the sample of patients form May 2013 to September 2013 through a recalling program. To eliminate possible bias, the examiner was not directly involved in the procedures during patients' rehabilitations.

Inclusion criteria

Only patients who presented partial edentulism and underwent localized horizontal or vertical alveolar ridge augmentation procedures with particulated grafts for implant rehabilitation purposes were admitted to the present study.

Exclusion criteria

Patients presenting poor oral hygiene, active periodontal infections, uncontrolled systemic pathologies and presence of smoking habit (> 10 cigarettes/day) were not treated with GBR procedures and therefore were not enrolled in the present study.

Clinical evaluation

During the clinical evaluation, only implants still present in the mouth (censored) at the end of the observation period, with no signs of mobility, periimplantitis and symptoms such as pain and/or altered sensation were considered survived [6, 19]. For each patient, a record containing the source of the graft (autologous, xenogenous or a mixture of autologous and xenogenous), the type of membrane (bioabsorbable or non-resorbable), the timing of implant insertion (simultaneous or delayed) and the date of implant loss was filled out.

Statistical analysis

The statistical analysis was performed using the Statistical Package for Social Sciences (version 21.0, SPSS Inc., Chicago, Illinois, USA). Kaplan–Meier survival analyses were done for the complete group of implants and discriminated according to type of grafting materials, membranes used and timing of implant placement. Log rank tests were utilized to compare the survival rate for implants in each of the subgroups. P values less than 0.05 were considered to be statistically significant.

Results.

A total of 192 implants inserted in 37 female and 24 male patients were retrospectively evaluated. 76 implants were placed in particulated demineralized bovine bone mineral (DBBM) graft (Bio-Oss®; Geistlich Pharm AG, Wolhausen, Switzerland), 20 in particulated autogenous bone graft and 96 into a 1:1 ratio mixture of autologous and DBBM particulated graft. 101 grafted sites were covered with resorbable membranes (Bio-gide®; Geistlich Pharm AG, Wolhausen, Switzerland) while 91 were protected with non-resorbable expanded polytetrafluoroethylene (e-PTFE) membranes (Gore-Tex; W.L. Gore & Associates, Flagstaff, AZ). 95 implants were positioned simultaneously with the GBR surgery, whereas 97 implants were inserted according to a delayed approach 6 months after the surgery (figure 1-10). Among the 192 implants positioned, a total of 5 implant failures occurred. Over a median follow-up period of 78 months (range 1-175 months) the cumulative survival rate (CSR) was 95,6% (figure 11). In regard to the source of the bone graft, in the DBBM group 2 failures occurred and a CSR of 95,0% was reported. One failure occurred in the autogenous group, showing a CSR of 93,3%. Two implants failed in the mixed group, leading to a CSR of 97,7% (figure 12). Considering the type of membrane, the CSR was 96,5% when the surgical sites were covered with bioabsorbable membranes, whereas a CSR of 94,6% was reported when graft was protected with non-resorbable membranes (figure 13). With respect to the surgical approach, 2 implants failures occurred after one-stage procedures, and 3 implants failed after the two-stage approach. A CSR of 96,8% was found in the simultaneous approach, while a CSR of 94,5% was reported in case of a delayed approach (figure 14). No Log rank statistically significant differences (p>0,05) could be found among source of graft, type of membrane and implant placement timing variable groups (Table 1).

Discussion.

The purpose of the present study was to assess the CSR of 192 implants placed in association with GBR procedures, and to evaluate the influence of source of graft, type of membrane, and timing of the surgical procedure on the results. A CSR of 95,6% over a mean follow-up of 78 months was calculated. This was in accordance with the principal studies currently available in literature[20-22]. In a recent review proposed by Clementini et al., taking into consideration the CSR of implants inserted in alveolar ridges augmented with GBR procedures, a range from 93,7% to 100% was noticed in all of the analyzed studies, with a follow-up ranging between one and 7 years. It was therefore assumed that GBR could be a predictable technique for implant placement purposes in atrophic sites [23]. A further review by Simion et al.[18] reported a CSR concerning vertical GBR ranging from 92,1% and 100%, up to a 7 years follow-up period. Kostantinidis et al.[6] found a CSR of 97,3% with implants placed in resobed ridges using a simultaneous GBR procedure 1 year after loading independently from the membrane adopted. Similarly, Bazrafshan et al. [24] in a recent manuscript, observed a cumulative survival rate of 97,5% evaluating 59 implants with a mean follow-up of 35 months.

Regarding the estimated CSR of implants inserted in regenerated sites depending on the type of bone grafts, independently from the type of barrier membrane, a CSR of 97,7% was achieved with autologous and DBBM grafts mixed together; 95,0% when DBBM graft alone was chosen, and 93,3% when only autologous bone was preferred. Several studies revealed a CSR ranging from 92,6% to 100% concerning implants placed in sites regenerated with xenografts or autografts used alone or mixed together [25]. Chiapasco et al., in a systematic literature revision, investigated studies in which GBR procedures were applied to correct peri-implant defects [26]. From the research, 5 prospective [25, 27, 28 29, 30] and 2 retrospective studies [31 32] were included. A

total of 238 patients received 374 implants placed in conjunction with different type of grafts and membranes. The overall survival rate was 95,7% with a minimum value of 84,7% and a maximum value of 100%, after at least one year of follow-up. It could be assumed, as confirmed by other studies [15, 33, 34] that xenogeneic and autologous grafts mixed together provided better results in terms of newly formed bone amount, probably due to the fact that the intrinsic osteoconductive properties belonging to the DBBM could reduce the physiological bone resorption induced by the natural remodeling [15, 34]. Even if the present data were not statistically significant, the 1:1 ratio autogenous/DBBM mixture offered slightly superior outcomes when CSR were compared. Aware of the intrinsic proprieties of both materials, in case of a simultaneous approach only limited amount of autogenous particles facing the implant surface toward the dehiscence may be needed, as DBBM characterized by a slow substitution time, could be employed to cover and protect the autograft during the remodeling phase.

Relating the CSR with the type of membrane disregarding the type of bone graft and the timing of implant placement, a CSR of 96,5% was observed for bioabsorbable membranes, while a CSR of 94,6% was noticed for non-resorbable membranes. Zitzmann et al.[25] analyzing 41 implants treated with non-resorbable membranes, found a CSR of 92,6% after a mean follow-up of 5 years; contextually, a total of 112 implants placed in conjunction with resorbable membranes showed a 95,4% CSR. Blanco et al.[27] considering 26 implants presenting fenestrations or dehiscences managed with non-resorbable membranes, achieved a CSR of 96,1% over a 5 years follow-up period. Finally, Jung e Coll.[17] evaluating 153 implants placed in combination with GBR techniques, reported a CSR of 91,9% for bioabsorbable membranes and 92,6% for non-resorbable membranes, with a mean follow-up of 12,5 years. Considering the type of membrane, non-statistically significant superior outcomes were found when bioabsorbable barriers were

considered. The employment of resorbable or non-resorbable membranes was clinically dictated by the criticism of the bony defect. The current orientation of the authors was to extend the employment of collagen barriers even in wide defects. Indeed, in authors' opinion fixing and tightening bioabsorbable membranes with bone pins may prevent early dislocation of the barrier increasing the stability of the graft and the conservation of the desired bone volume with results comparable to those reported for non-resorbable membranes.

Regarding the timing of implant placement, without considering the type of graft and membrane used, a CSR of 96,8% emerged from one-stage procedures, whereas a rate of 94,5% was observed in case of a delayed approach. Similarly, Cordaro et al. reported a mean implant survival rate of 98.9% and 100% when simultaneous and staged GBR were respectively assessed [1]. Zitzmann et al. revealed a CSR in regenerated sites with a one-stage procedure in conjunction with bioabsorbable membranes of 95,4%, while a CSR of 92,6% was found when non-resorbable membranes were used [25]. High survival rate ranging from 91.9% to 92.6% were also reported by Jung et al. considering 265 implants placed simultaneously with GBR procedures using resorbable or non-resorbable membranes [17]. A cumulative survival rate of 97.2% after 12 months of loading was reported by Konstantinidis et al. evaluating 36 implants placed simultaneously with GBR surgeries [6]. With respect of staged GBR, survival rate of 99–100% for observation periods ranging from 22.4 months to 5 years post-loading was reported [19]. Data emerged from the literature emphasized the relevant reduction of possible implant failures a two-stage approach was considered [35]. The grafted bone may spontaneously heal throughout a sufficient period of time, without being altered by external events or possible interferences caused by the presence of implants. During an adequate healing time, a remodeling process occurs, resulting in an incorporated mineralized bone, which enhances the osteointegration percentage of the implants

at the recipient site. Furthermore, the staged approach could represent a suitable alternative especially in case of severely atrophic bone defects, due to the fact that during the second surgery, clinicians would be able to evaluate the entity of the reconstruction obtained and eventually perform a further regenerative procedure. As the results reported in our study were not statistically different, there was no evidence to affirm whether the simultaneous or the staged approach may be considered the "gold standard" to obtain the most predictable amount of regenerated bone associated with GBR. Since the one-stage protocol obtained comparable results in terms of implant CSR, simultaneous surgery should be suggested when the native bone is adequate to place implants in the correct position. Consequently, the number of surgeries and the time needed to finalize the rehabilitation could be reduced to a minimum.

Conclusions.

According to the survival rate analysis conducted in the present study, implants placed in conjunction with GBR procedures presented encouraging results even in the long-term period.. A statistically significant difference comparing each predictor of implant failures could not be found. The use of DBBM combined with resorbable membranes may avoid the harvesting procedure and the re-entry surgery reducing the post-operative morbidity for the patient and the treatment time. Further long-term studies will be necessary to widen the potentialities of DBBM and resorbable membranes in the reconstruction of extended bone defects simultaneously with implant placement.

Acknowledgments.

We declare that we did the work without receiving any financial support from any third party.

Table 1. The significant P values for each recorded group

GROUPS	Sig. P values.
GRAFT (autograft - xenograft - 1:1 mixture)	.93
MEMBRANE (resorbable - not resorbable)	.65
SURGICAL APPROACH (one stage - two stage)	.52

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Figure References

Figure 1: Radiographic investigation underline apical lesion at the left upper central incisor.

Figure 2: Clinical preoperative evaluation of central upper incisor**.**

Figure 3: Surgical guided device for placing dental implant in ideal prosthetic position**.**

Figure 4: Bone defects underlined after the flap opening.

Figure 5: Dental implant positioning following the ideal prosthetic position. Horizontal and Vertical bone defects can be easily underlined.

Figure 6: Bone regeneration by using a mixture of autologous bone and deproteinized bovine bone is applied on the defect**.**

Figure 7: a PTFE reinforced on titanium has been applied for doing GBR technique**.**

Figure 8: 6 months after the first surgery, the second surgery for removing the membrane shows the consistence of the new bone volume.

Figure 9: Final crown restoration**.**

Figure 10: 3 years follow up clinical control**.**

Figure 11: Survival Rate.

Figure 12: Survival Rate considering grafts.

Figure 13: Survival Rate considering membranes.

Figure 14: Survival Rate considering procedures.

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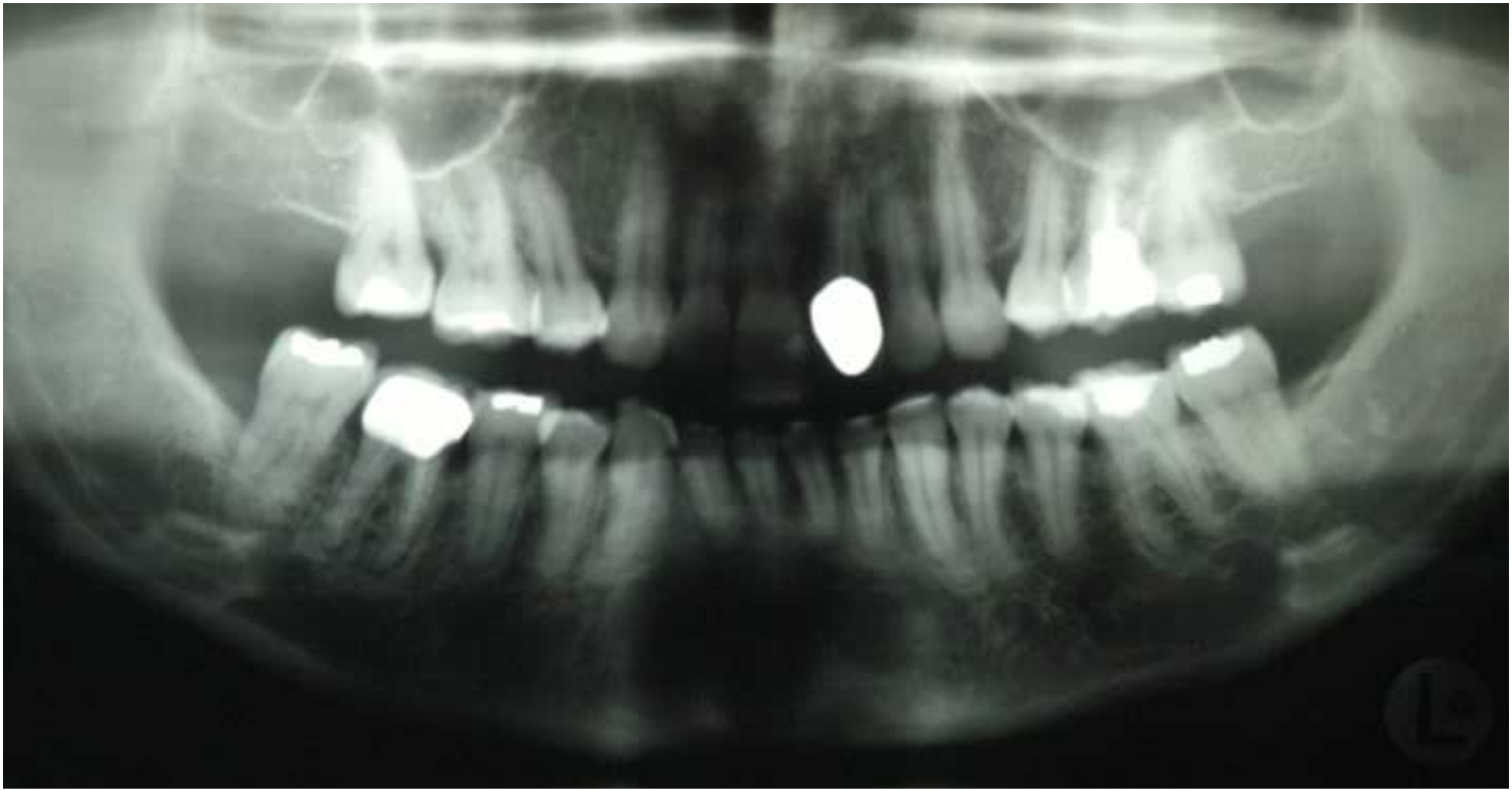

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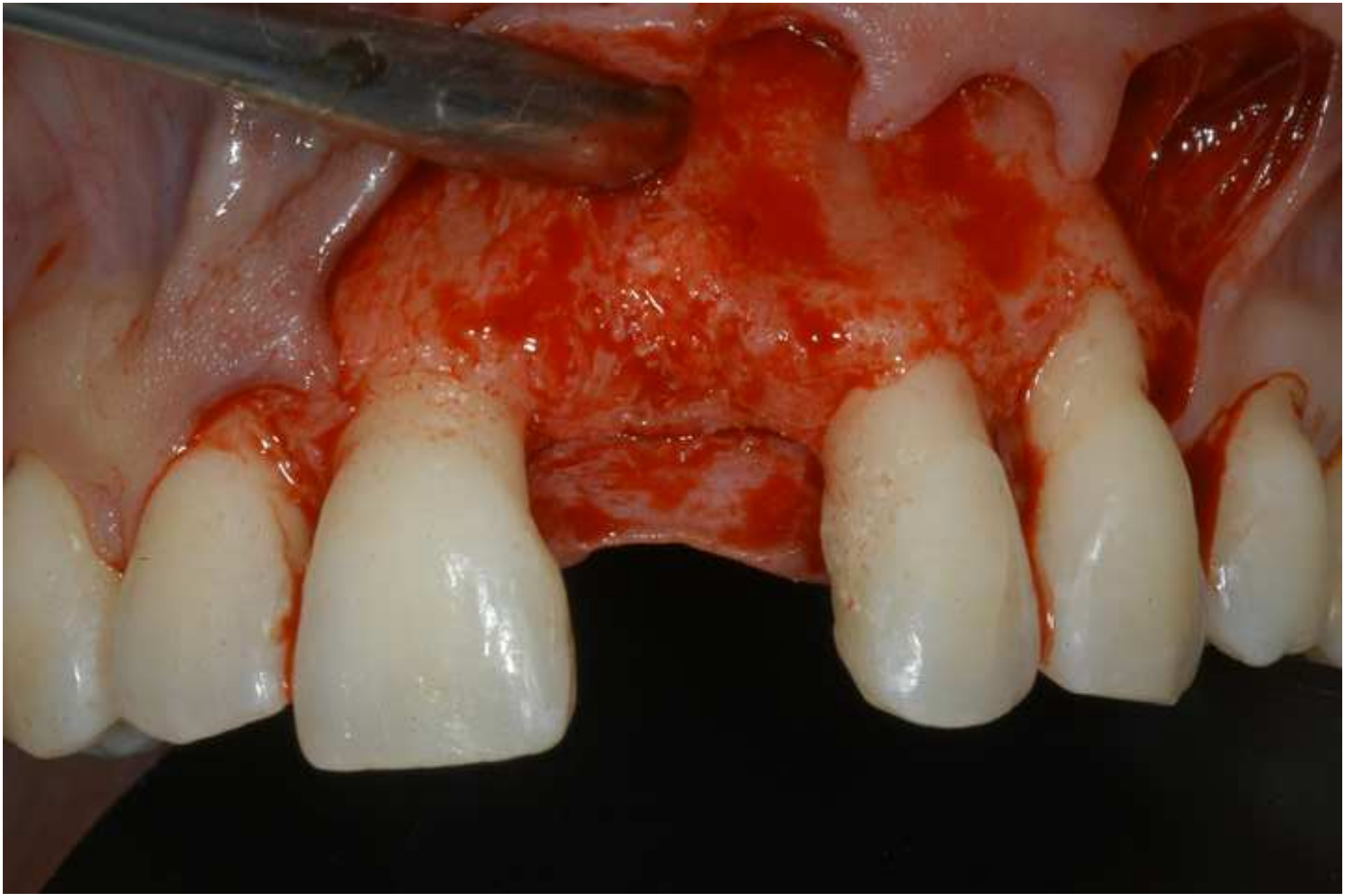

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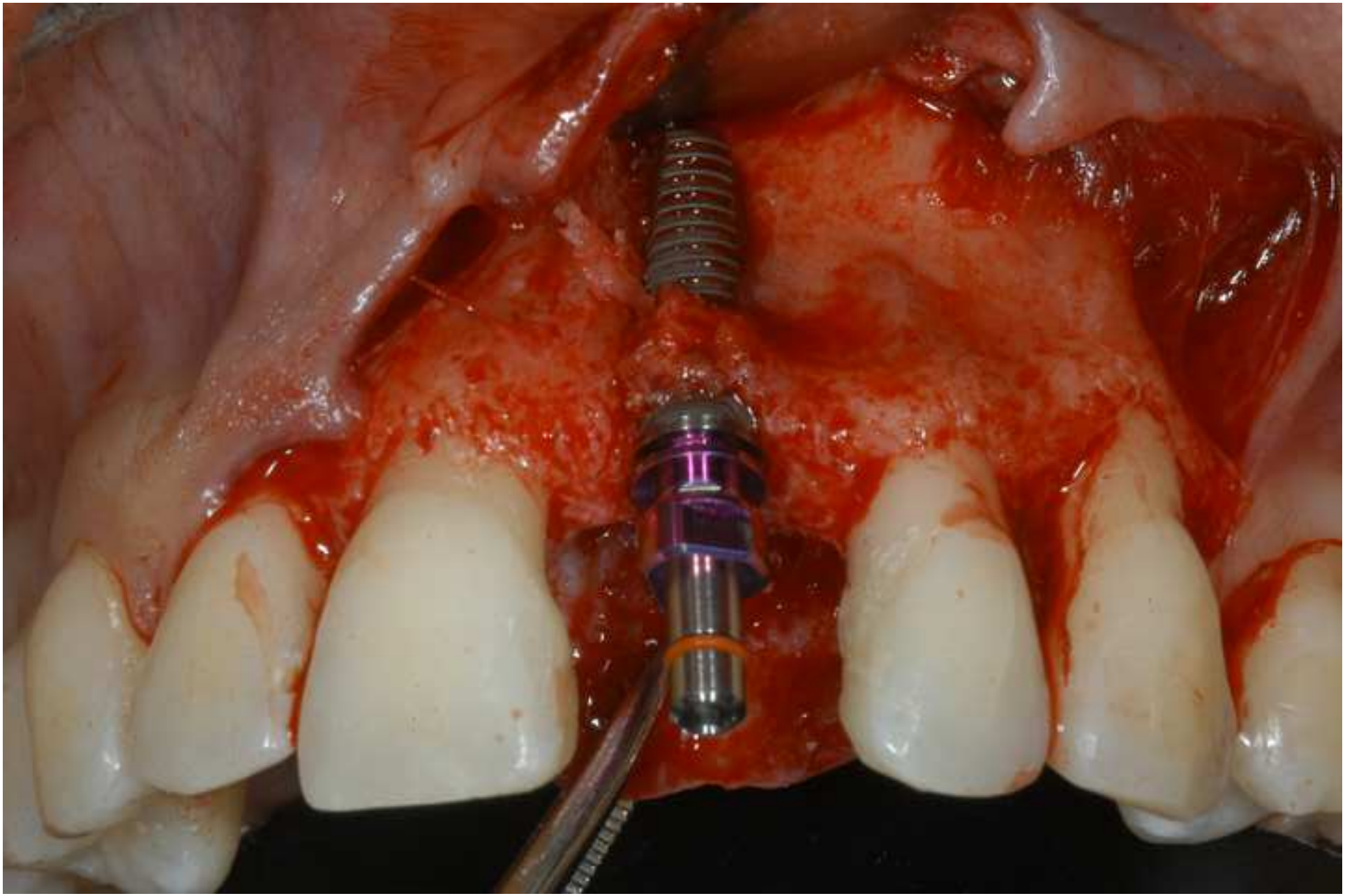

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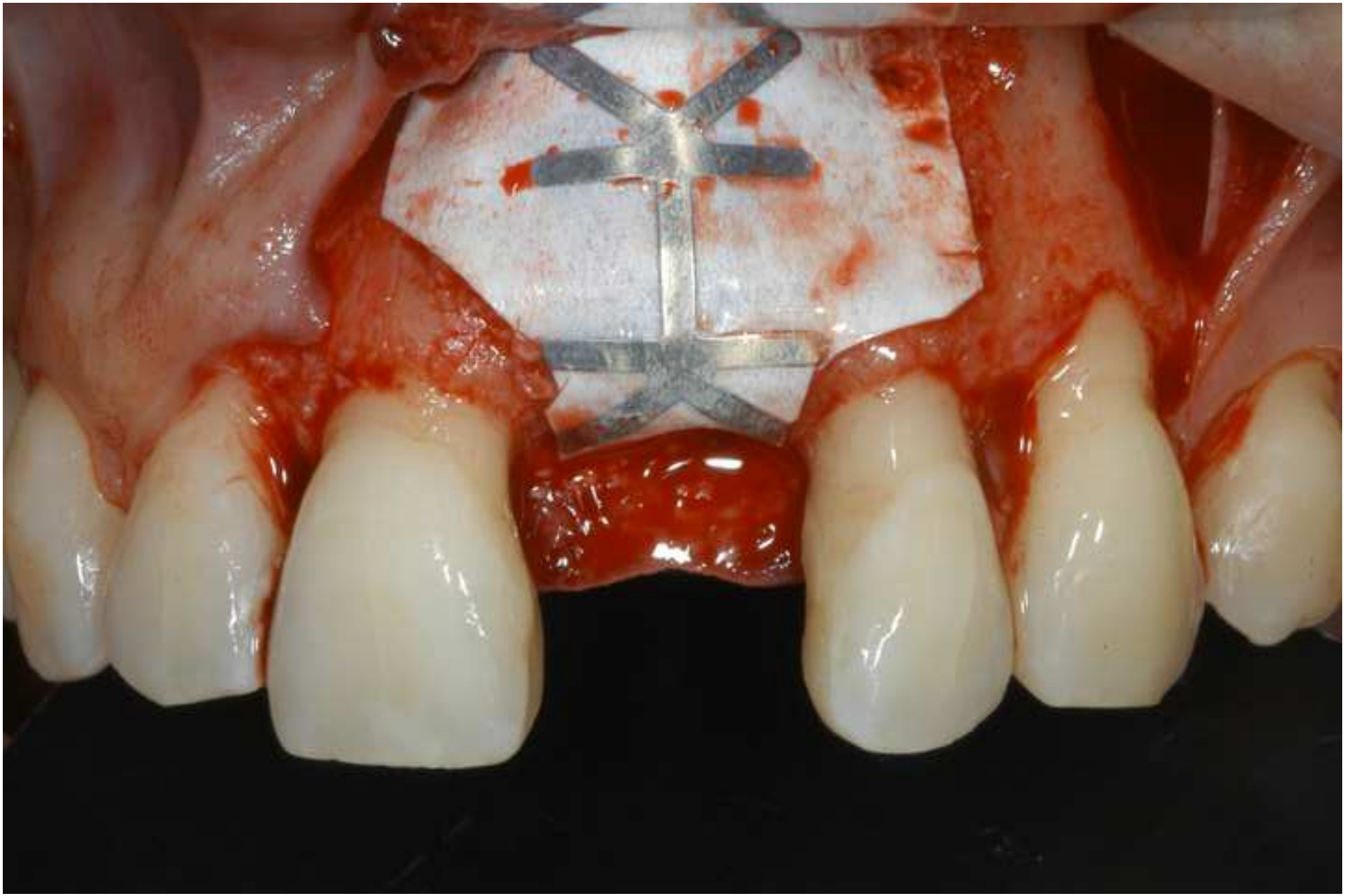

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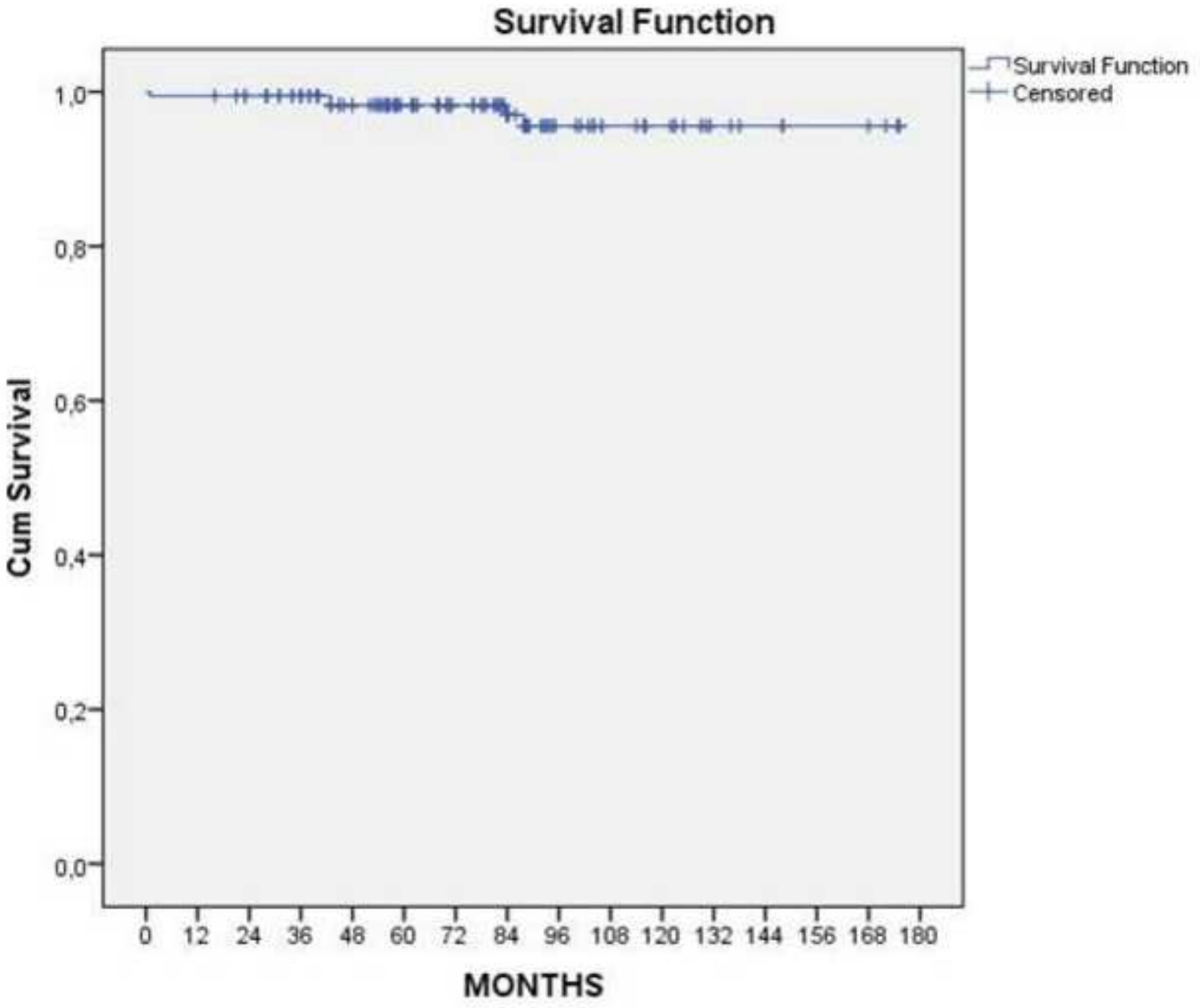

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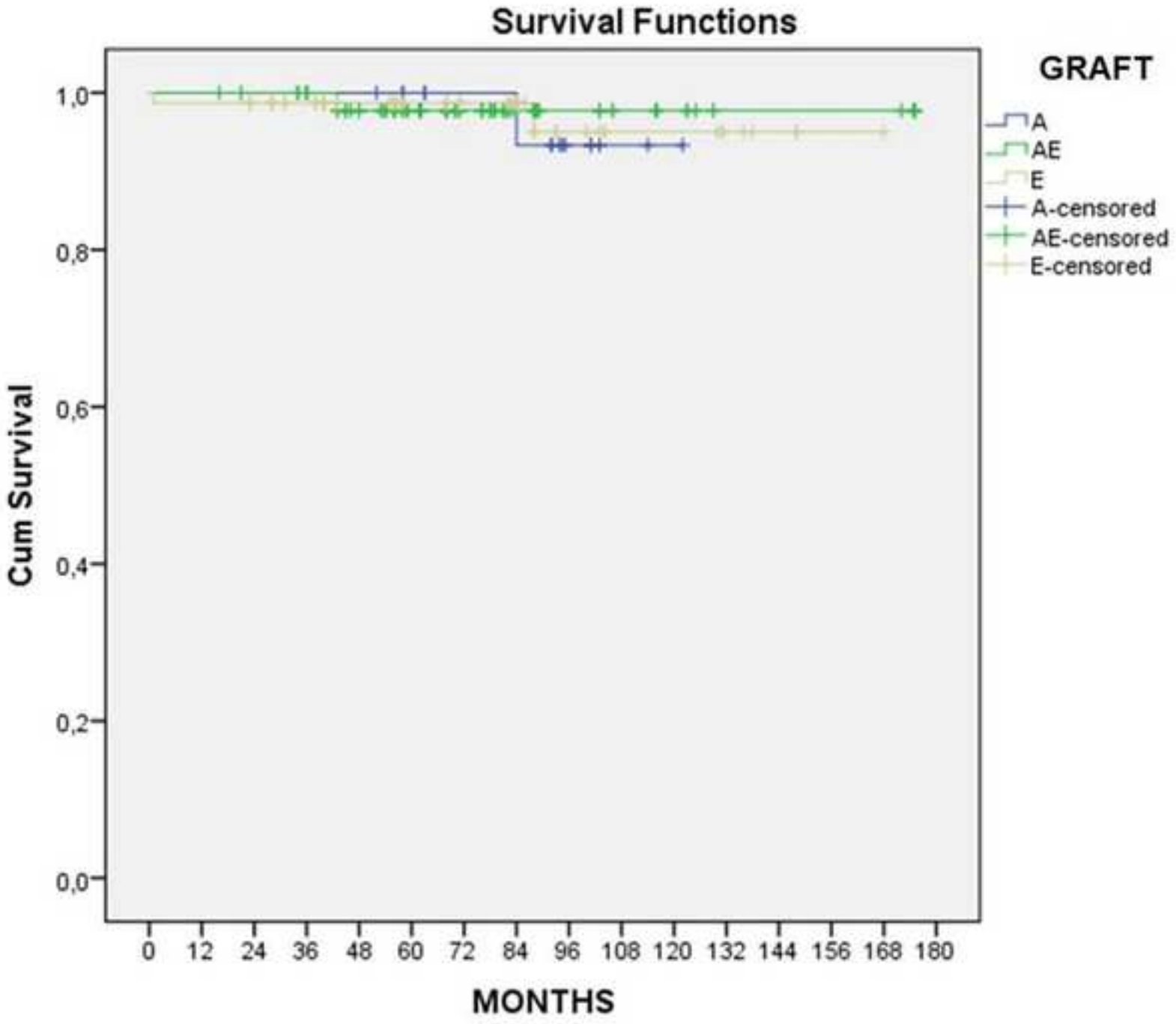

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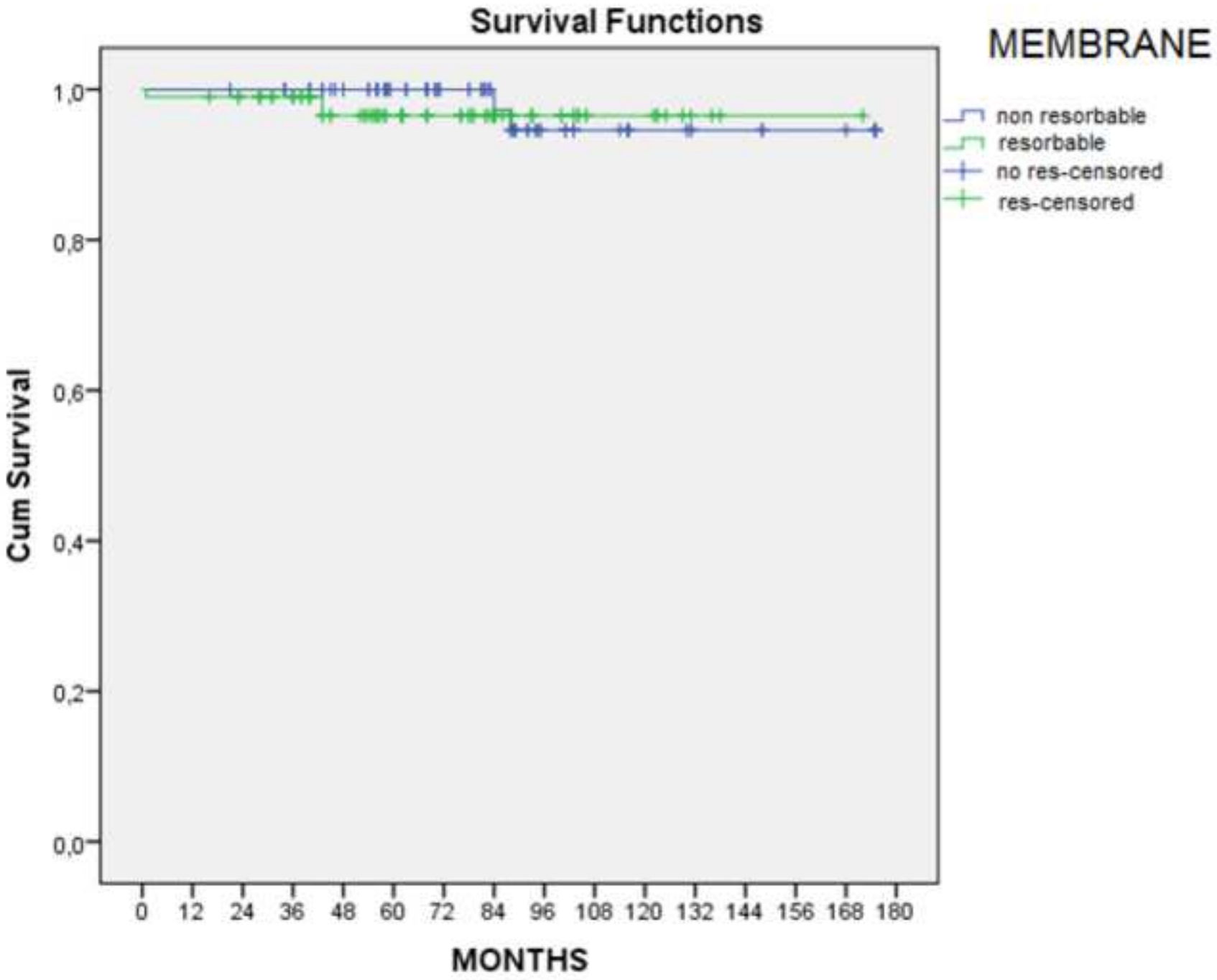

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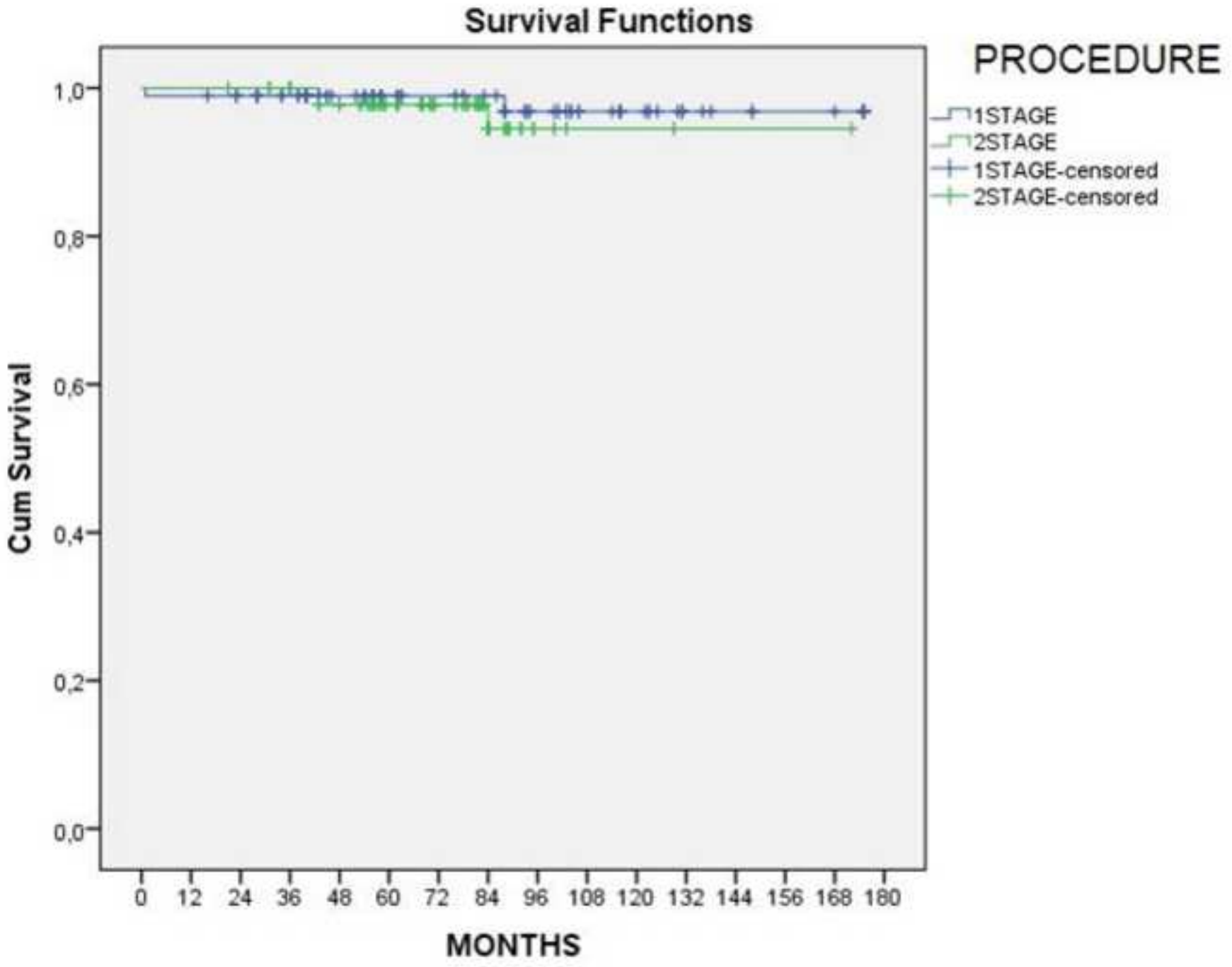

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