A Study on Variances in Multivariate Analyses of Oral Implant Outcome

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ABSTRACT

Background: Elaborate studies have shown that interdependency exists between implants being placed in the same patient/jaw. Therefore, interdependency ought to be an important aspect to address, whenever performing statistical analyses of oral implant outcomes. A Jackknife method could be an option when conducting statistical evaluations of oral implant failure prognoses.

Purpose: The aim of this study was to evaluate whether a statistical difference can be detected by using the Jackknife method in conjunction with life table analyses and/or a log rank test of four different combinations of jaw density and quantity.

Materials and Methods: Four multicenter studies were pooled and adjusted in order to create a research database consisting of 486 patients and 1,737 implants in preparation for the Jackknife resampling method. Combinations of jaw shapes and bone qualities were constructed to select at-risk patients.

Statistical Methods: Life tables with confidence intervals were calculated and a log rank test was used to determine whether a statistical difference between the combinations could be established.

Results: Both statistical analyses, after the Jackknife resampling method, showed that patients with poor bone quality and resorbed jaws (combination IV) had a statistically higher risk of implant failure.

Conclusion: By rearranging data using the Jackknife method, standardized statistical tests seem to work well even when the study population tested was affected by interdependency.

KEY WORDS: dental implants, interdependency, Jackknife, life table analysis, log rank test, statistical analysis

Publications on the use of oral implants have proliferated immensely over the last decades and about 1,000 new reports on this topic are currently presented annually in *PubMed*.[1] Most of these publications focus on new features of certain implant brands, and statistical analyses used often vary from purely descriptive reports to advanced multivariate tests, with or without taking interdependency into account. Elaborate studies performed by Herrmann and colleagues[2] and others[3–5] have shown that there may be interdependency between implants being placed in the same patient/jaw. Consequently, interdependency ought to be an important aspect to consider and address whenever performing statistical analyses of oral implant outcomes.

It was thus notable that Chuang and colleagues[6] could not demonstrate any difference in the implant failure outcome when they ignored interdependency in their statistical test. However, in a subsequent article[7] on implant failures, the same authors still used multivariate analyses with interdependency being taken into account. Eckert and Wollan[8] and Eckert and colleagues[9] proposed a similar procedure whereby a robust standard error (SE) method was used to handle the interdependent data. Chuang and colleagues[10] later improved these methods, constructing robust variance–covariance estimators by modelling implant failure times with the Cox proportional hazard model. They used the model to account for possible intraclass correlations purported to exist among dental implants within the same individual.

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When evaluating data suspected to be affected by interdependency, other statistical methods, for example, Bootstrap[11] and Jackknife,[12] can be used when performing multivariate analyses. The Jackknife method, for example, allows judging uncertainties of estimators derived from small samples without making assumptions about the underlying probabilities of the distribution. In this way, all inserted implants can be included in the statistical analysis without ignoring established interdependency within the patients' jaw.[2] Furthermore, the technique also allows for combinations of life table or log rank test analyses.

Consequently, the Jackknife method ought to be an option and an alternative to the previously used[2,13] method for randomly selecting one implant per patient/jaw before conducting statistical evaluations of oral implant failure prognoses.

The aims of the present investigation were:

1. to estimate variances and SEs of risks of implant failure in relation to combinations of jaw qualities and quantities (jaw shapes) by using a Jackknife method in conjunction with life table analysis of all inserted implants, and
2. to evaluate whether a statistical difference can be detected when using the Jackknife method in conjunction with a log rank test, using the same combinations of jaw qualities and quantities as well as number of implants.

MATERIALS AND METHODS

Original Study Population

Four multicenter (MC) research studies, each reporting on screw-shaped implants with a turned surface (Brånemark System®, Nobel Biocare AB, Göteborg, Sweden), constituted the basis of the present statistical study. Patient categories included single-tooth loss,[14] partially edentulous patients,[15] and edentulous patients restored with either overdentures[16] or fixed prostheses.[17] All studies followed similar treatment protocols in the maxilla or mandible and received a total of 1,738 implants. The four MC studies were conducted in accordance with guidelines for clinical research accepted at the time, including the Helsinki declaration and the criteria established for the handling of patient databases.[18,19] The aims of the four studies had been to assess the number of complications and to evaluate the cumulative success rates (CSR) of implants monitored during a 5-year period of clinical function, based on slightly modified success criteria described by Albrektsson and colleagues.[20,21] Detailed articles reporting surgical and prosthetic protocols, follow-up routines, and outcomes of the separate studies were presented earlier.[14–17,22–25]

Pooled Study Population

The four MC patient groups were pooled to create a new database of 487 patients. Forty-seven percent of these individuals were females, and the mean age of the entire group was 51 years (range, 15–84 years). Of the patients treated, 42% received implants in their upper jaw. Two hundred thirty-six patients were completely edentulous from the start, while the remaining 251 patients had one or several missing teeth needing replacement. Additional information was collected after the four studies had been concluded by contacting the original authors to request clarification of inconclusive data in the original studies of implant-related events and time periods. The information provided was then included in the pooled material, giving a more accurate database. However, neither the total number of inserted (n = 1,738), failed (n = 110), and unaccounted for implants (n = 323), nor the number of included patients (n = 487) was affected by these corrections.

Only factors that in previous studies had shown a statistical difference between compared groups were evaluated in the present elaboration. Consequently, patient gender and age, responsible doctors/clinic, and numbers of implants supporting the restorative construction were not further analyzed.[13]

For all pooled patients, except the single-tooth replacements, jawbone quality (density) and jaw shape (quantity) had been analyzed according to Lekholm and Zarb[26] in the original studies. However, the single-tooth patients were only categorized with regard to bone quality. In order to be able to classify this variable in the single-tooth patients, their jaw shape was assessed by the length of implant inserted. To score jaw shapes from A (most bone available) to E (extremely resorbed bone),[26] the following approximations were made and added to the pooled database. When a 7-mm implant was placed, the jaw shape was assumed to belong to group E; 10 mm was judged as group D, 13 mm as group C, 15 mm as group B, and 18 mm or longer as group A, respectively.

Combinations of jaw shapes and bone qualities were constructed in order to further select extreme at-

TABLE 1 Distribution of Randomized Subgroups and Number of Patients in Preparation for Jackknife Resampling,[12] Regarding Inserted Implants per Combination of Jaw Qualities[26]/Jaw Shapes[26], Respectively

		Jaw-Quality/Jaw-Shape Combinations[13]			
Randomized Subgroups	Number of Patients	1, 2, 3/A, B, C	1, 2, 3/D, E	4/A, B, C	4/D, E
1	54	162	9	12	6
2	54	147	22	29	4
3	54	135	22	27	14
4	54	151	46	7	0
5	54	131	29	25	0
6	54	173	13	10	0
7	54	143	28	16	7
8	54	139	32	11	2
9	54	130	32	16	7
Total	486*	1,311	233	153	40

*One successfully treated single-tooth patient was excluded from the pooled study population to achieve equally sized patient groups.

risk patients regarding prognostic implant failure, in the way described by Herrmann and colleagues.[13] The bone combinations were determined by establishing significant differences between jaw shape (two groups) and bone quality (two groups), based on the risk of implant failure. These four groups resulted in four different jaw shape/quality combinations (combinations I–IV), where combination I consisted of implants placed in good bone quality and jaw shapes (A, B, C/1, 2, 3), that is, in combinations related to a low risk of implant failure in the previous report.[13] Combination II consisted of implants placed in jaw shapes with lower success rates, but in good bone quality (D, E/1, 2, 3). Combination III consisted of implants placed in jaw shapes related to a higher success rate, combined with poor bone quality (A, B, C/4). Finally, combination IV consisted of implants placed in bone combinations showing the highest failure rates (D, E/4).[13]

Research Population

The newly pooled and corrected database was then prepared for the Jackknife resampling method[12] of the patients by creating nine equally sized randomized subgroups. One single-tooth patient representing a successful outcome was excluded ($n = 487 - 1$) in order to obtain an equal number of patients ($n = 54$) in each subgroup. Before allocating the patients to the nine subgroups, a randomization chart[27] was adjusted so that an almost equal distribution of patients from the various MC studies could be obtained, allowing a maximum discrepancy of two patients/MC study. Each patient was then manually allocated, regardless of the number of implants inserted. The distribution of implant numbers across combinations I to IV showed that the majority of the implants (1,311) were inserted in combination I, while only 40 implants were inserted in combination IV (Table 1). Furthermore, the randomization of the patients in combination IV demonstrated a range of 0 to 14 implants/subgroup. The numerical distribution of implants inserted-location, and failures (in percent) can be seen in Table 2.

STATISTICAL PREREQUISITES AND METHODS

In order to perform the subsequent statistical calculations, the patients included in the current research population were assumed to be independent of each other. Furthermore, within each patient, interdependency had to be taken into account between implants inserted and monitored, as previously recognized.[2–9,13]

Finally, in spite of the defined dependency, the population was considered large enough to use approximated normality for a significant evaluation, regarding the log rank test used subsequently.

Life Table Analyses

The CSRs for different time periods were calculated for all implants inserted and monitored in the research population (486 patients and 1,737 implants) using life table analysis according to Kaplan and Meier.[28] Six preset time periods were evaluated (Table 3), spanning from before

TABLE 2 Distribution of Randomized Subgroups and Number of Patients in Preparation for Jackknife Resampling,[12] Regarding Inserted Implants per Maxillae and Mandible, and Regarding Total Numbers of Inserted and Failed (%) Implants, Respectively

		Implant Distributions			
Randomized Subgroups	Number of Patients	In Maxillas	In Mandibles	Inserted	Failed (%)
1	54	65	124	189	4.2 (n = 8)
2	54	33	169	202	8.9 (n = 18)
3	54	80	118	198	9.6 (n = 19)
4	54	103	101	204	7.4 (n = 15)
5	54	46	139	185	7.6 (n = 14)
6	54	65	131	196	2.0 (n = 4)
7	54	88	106	194	8.2 (n = 16)
8	54	73	111	184	3.3 (n = 6)
9	54	69	116	185	5.4 (n = 10)
Total	486*	622	1,115	1,737	6.3 (n = 110)

*One successfully treated single-tooth patient was excluded from the pooled study population to achieve equally sized patient groups.

loading of the implants until 5 years of clinical function. Life table analysis was also utilized to evaluate the CSRs for the various jaw shape and quality combinations (combinations I–IV).

Jackknife Resampling Method

Prior to conducting any statistical test, the Jackknife resampling method according to Quenouille[12] was used to evaluate the risks of implant failure over time for combinations I to IV. For this purpose, each of the nine equally sized and randomized subgroups (n = 54 patients) was individually excluded (Figure 1), resulting in samples of the 432 remaining patients (see Table 3). In this way, nine samples were produced to estimate the variances for derivation of SEs and confidence intervals (CIs).

Variances, SEs, and CIs

The variances from the Jackknife samples were used to demonstrate the uncertainty of the CSRs representing the six time periods (before loading to 5 years of clinical function) and the different combinations I to IV of jaw shape and quality. The sample variances were calculated from an average squared deviation of each CSR. The SEs for the CSRs of the entire research population

TABLE 3 Life Table Analyses Regarding Cumulative Implant Success Rates, Based on the Research Population of 486 Patients and 1,737 Implants, Obtained and Restructured from the Four Multicenter Studies,* and in Relation to Time Periods Studied

Time Periods	Years after Implant Placement	Total No. of Implants at Start of the Period	No. of Failures Within Period	No. of Implant Lost to Follow-Up Within Period	Cumulative Success Rates (%)
1	Placement loading	1,737	44	47	97.5
2	Loading†–1 year	1,646	37	57	95.3
3	1–2 years	1,552	14	54	94.4
4	2–3 years	1,484	7	36	94.0
5	3–4 years	1,441	2	59	93.8
6	4–5 years	1,380	6	70	93.4
	5 years	1,304			

*Single crowns in jaws with single gaps[14]; fixed bridges in partially edentulous jaws[15]; overdentures in edentulous jaws[16]; full fixed bridges in edentulous jaws.[17]
†Unloaded implants were included during the entire follow-up period.

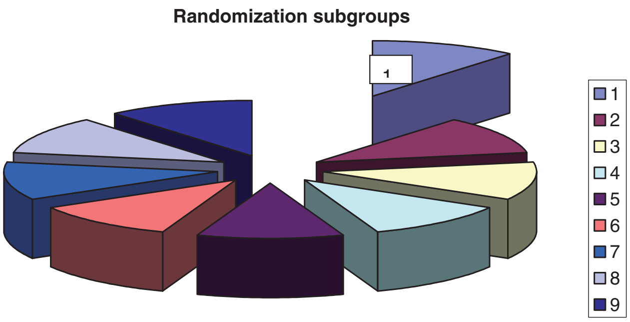

Figure 1 Pie chart showing the principle of creating Jackknife resampled groups.[12] 1, the randomization subgroup 1 ($n = 54$ patients) has been excluded, while the eight other subgroups remain (432 patients).

were calculated from these estimated variances. The CIs for the CSRs were calculated by applying the SEs given by the estimated variances to the CSR means. Then the CSRs for combinations I to III (test group I) were combined to test whether a statistical difference from combination IV (test group II) could be detected.

Log Rank Test

A standardized log rank statistic test,[29] by definition, uses a ratio in which the numerator is an estimate of the survivorship based on excess failure number, and the denominator is an estimate of the SE.

The log rank test was used as an alternative statistical method to test for differences in the survival distribution between the two test groups (combinations I–III vs IV). The log rank test uses the number of implants "at risk" at each time period (those still in function) in each group and in total to predict the number of failures in each group. The difference between the predicted and actually observed number of failures is then calculated at each time period and summed over the six time periods, the "excess failure number." In this study, the log rank test was performed after the Jackknife resampling method but also without using the Jackknife method, to estimate the difference between the two predictions due to interdependency.

RESULTS

Life Table Analyses

Life table analysis of the 1,737 implants placed in the 486 patients of the research population yielded a CSR of 93.4% (see Table 3) after 5 years of clinical function. The corresponding CSRs for the bone quality/quantity combinations were 95.3% in group I, 92.1% in group II and 90.2% in group III, but 54.8% for combination IV (Table 4). Note that the CSR for combination IV before loading was approximately 20% lower than the other combinations and continued to decrease another 22% during the 5-year period studied. Combinations I to III, on the other hand, all displayed CSRs higher than 90% after 5 years, decreasing 2.9% to a maximum of 5.9% from the before-loading values.

Jackknife Resampling Method

Within the nine subgroups (each of 54 patients) used in preparation for the Jackknife method, the number of implants in the four jaw-shape/bone-quality combinations varied from 0 to 173 implants (see Table 1). A corresponding variation of upper or lower jaw (see Table 2) was also seen, from 33 implants in the maxilla and 169 in the mandible in one subgroup, to 103 and 101 implants in another. However, the total number of implants within the subgroups only varied from 184 to 204 implants (see Table 2), and the failure rates within the subgroups varied from 2.0% to 9.6% (mean 6.3%).

TABLE 4 Distribution of Cumulative Success Rates (%) Obtained from Life Table Analyses, Based on the Research Population, Regarding the Combinations I to IV[13] (Jaw Shape[26]/Bone Quality[26]), and in Relation to Time Periods Studied

Time Periods	Years after Implant Placement	Combination I (%)	Combination II (%)	Combination III (%)	Combination IV (%)
1	Placement loading	98.2	97.4	96.1	77.5
2	Loading*–1 year	96.7	94.3	94.0	60.0
3	1–2 years	95.8	94.3	91.8	57.4
4	2–3 years	95.7	92.1	91.8	57.4
5	3–4 years	95.6	92.1	91.8	54.8
6	4–5 years	95.3	92.1	90.2	54.8

*Unloaded implants were included during the entire follow-up period.

TABLE 5 Distribution of Standard Errors for Survival Probabilities Calculated on the Jackknife Samples[12] for the Combinations I–IV[13] (Jaw Shape[26]/Bone Quality[26]), and in Relation to Time Periods Studied

Time Periods	Combination I	Combination II	Combination III	Combination IV
1	0.00367	0.00116	0.02368	0.05107
2	0.00836	0.02338	0.02960	0.06193
3	0.00810	0.02338	0.03582	0.07795
4	0.00751	0.02617	0.03582	0.07795
5	0.00743	0.02617	0.03582	0.07963
6	0.00877	0.02617	0.03239	0.07963

Furthermore, the uneven distribution of implant failures per subgroup also indicated a dependency within the patients.

Variances, SEs, and CIs

The SEs for implant survival probabilities calculated within the Jackknife samples (each of 432 patients) by time in function, and for the four jaw–bone combinations, are presented in Table 5. Before loading, the SEs ranged from 0.00116 for group I to 0.05107 for group IV. Considering all follow-up periods, the lowest SEs were found in combination I and the highest in combination IV (see Table 5). A diagrammatic presentation of the CIs and the CSRs over the six time periods for the two test groups can be seen in Figure 2. Test group I (combinations I–III) resulted in CSRs with 95% CIs, starting at 97.9% +/−1.5 and ending at 94.4% +/−1.6 after 5 years of clinical function. The corresponding figures for test group II (combination IV) were 77.5% +/−12.2 and 54.8% +/−15.9. No overlapping of CIs was seen at any time (see Figure 2).

Log Rank Test

The log rank test gave an excess failure number of 15.86 at the preset time periods, while the SE over the nine Jackknife samples groups was calculated to a value of 6.02. The ratio between the two numbers was 2.63, which corresponds to a one-sided p value of .015 for comparison of test group I and test group II. A significant difference on a level of .05 was thereby established between the two test groups (combinations I–III, IV).

The SE in the log rank test without using Jackknife resampling method was 1.43, giving a stronger significance level.

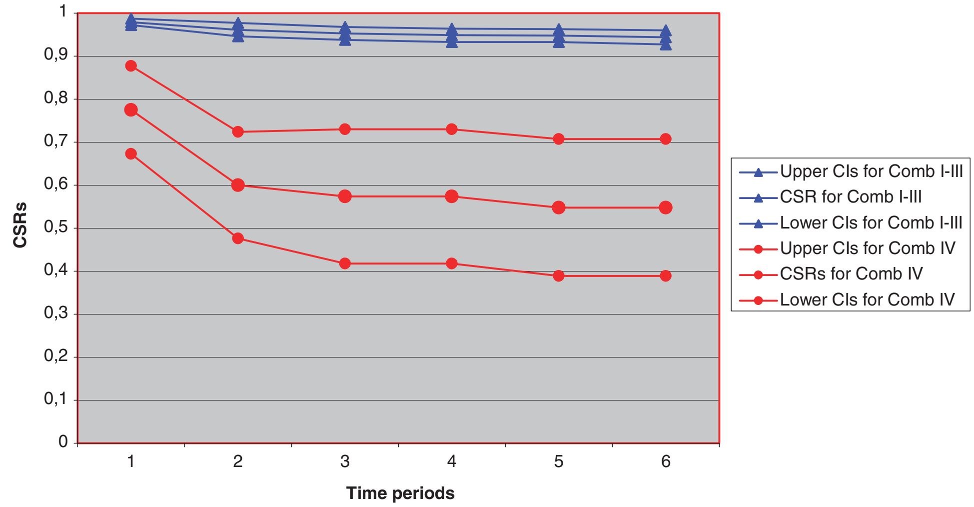

Figure 2 Diagram of the estimated cumulative survival rates (CSRs) and confidence intervals (CIs) for combinations I to III[13] and combination IV (jaw shape[26]/bone quality[26]), in relation to the time periods studied.

DISCUSSION

The current report clearly showed a statistical difference in the CSR between test groups I (combination I–III) and II (combination IV) (see Figure 2). The same outcome was also seen when the log rank test was used. Thus, the current study comparing all implants with the Jackknife resampling method coincides well with our previous statistical analyses[13] based on Pearson chi-square tests. That study, with one implant/patient also indicated higher risks of implant failure in patients with jawbone quality 4 and jaw-shape D or E (test group II).

Furthermore, the life table analyses of the current research population comparing by jaw–bone combinations clearly showed a lower success rate for test group II (combination IV) than test group I (combinations I–III) by adding CIs to the diagram (see Table 4 and Figure 2). Still, it is important to observe that the CRSs from life table analyses included all involved implants, while the CIs are calculated by using the Jackknife method. Life table analyses with CSRs are, on the other hand, one of the most frequently selected survival calculation methods used today to express failure or success prognosis for dental implant treatment.[30–32]

However, to use life table analyses alone to demonstrate statistical significances between two or more groups does not seem to be the best method of choice. Instead, CIs should be calculated as part of the statistical evaluation. Furthermore, CIs should be calculated when using the Jackknife resampling method' to account for established interdependency, as here.

In preparation for the Jackknife resampling method, nine equally sized subgroups, randomly selected, gave groups of 54 patients. Looking closer at the outcome of those subgroups, one further sign of interdependency within the research population was revealed as a difference in failure rates between the subgroups (see Table 2). Furthermore, the distribution of implants within the nine subgroups was uneven regarding the number of implants inserted in total, in the upper or lower jaw, or in the bone combinations (see Tables 1 and 2). Consequently, by combining eight of the nine subgroups each time, it was possible to obtain evenly sized patient samples including 1,533 to 1,553 implants inserted for the statistical analyses (Table 6).

TABLE 6 Distribution of Jackknife-Created Resamples[12] with Regard to Randomized Subgroups Included, Numbers of Patients, and Implants within Each Sample, Respectively

Jackknife Resamples	Included Randomized Subgroups	Number of Patients	Number of Implants
1	2–9	432	1,548
2	3–9 and 1	432	1,535
3	4–9 and 1–2	432	1,539
4	5–9 and 1–3	432	1,533
5	6–9 and 1–4	432	1,552
6	7–9 and 1–5	432	1,541
7	8–9 and 1–6	432	1,543
8	9 and 1–7	432	1,553
9	1–8	432	1,552

Alternative methods of handling interdependency have been suggested by Chuang and colleagues and others.[6–10] The Jackknife resampling technique for handling data with interdependency could, for example, have been replaced by the Bootstrap procedure.[11] However, no studies of dental implant outcomes with either the Jackknife nor the Bootstrap methods have been found in the *PubMed* reference lists.[1] Yet both methods are frequently used in pharmaceutical studies.[33–35] This study seems to be the first time such statistical techniques have been used to evaluate the outcome of oral implant treatment.

It was noted that the variances within the current report varied between the four combinations studied (see Table 5). One reason for this could be different numbers of implants inserted and failed within each combination. Another reason is that combination IV (test group II) was, with only 40 implants, much smaller than test group I (n = 1,697), which combined the three other jaw shape and bone quality combinations. Within test group I, combination I was likewise much greater, accounting for 1,311 implants. The reason for unequally sized groups was that the present research population was not originally designed for comparing the newly created fractions by sophisticated statistical methods.

To illustrate the importance of correctly considering interdependency, the SEs used in an ordinary log rank test, without using the Jackknife resampling method, were also calculated. The resulting ratio value (1.43) was only about 25% of the current Jackknife value (6.02). So using the ordinary log rank tests and assuming independence greatly underestimated the SE, and thereby a too strong significance level would have been established. This would be clearly not acceptable.

Certainly, the current data could have been evaluated by several other statistical methods. Neither Cox regression nor any multivariate analysis[6–10,36] was tested in this report, which instead focused on rearranging the data.

CONCLUSION

Several frequently used statistical methods have been shown to work sufficiently when studying the outcome of dental implant treatment as long as interdependency is acknowledged and addressed. The Jackknife resampling method of rearranging data affected with interdependency seems to work well when evaluating oral implant studies.

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