Exact and Asymptotic Tests for Sufficient Followup in Censored Survival Data

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Abstract

The existence of immune or cured individuals in a population and whether there is sufficient follow-up in a sample of censored observations on their lifetimes to be confident of their presence are questions of major importance in medical survival analysis. So far only a few candidates have been put forward as possible test statistics for the existence of sufficient follow-up in a sample. Here we investigate one such statistic, \(Q_n\), and give a detailed analysis assuming independence between survival and censoring times. We obtain an exact finite sample as well as asymptotic distributions for \(Q_n\), and use these to calculate the power of the test as a function of the follow-up in the sample. A particularly useful finding is that the asymptotic distribution of the test statistic is parameter free in the null case when follow-up is insufficient. The methods are illustrated with detailed schematic and real data sets, and the effect of dependence between survival and censoring is considered via a copula model and simulations.

Keywords Sufficient follow-up; censored survival data; cure model.

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1 Introduction

There is a large and growing interest in the analysis of censored survival data from a population which may contain immune or cured individuals, that is, individuals who will not experience the event of interest no matter how long follow-up may be. A systematic formulation and treatment of this kind of problem is in the book by Maller and Zhou (1996) which contains many practical examples from medicine, criminology and various other fields, of this kind of data. For other reviews and applications, see for example Amica and Van Keilegom (2018), Escobar-Bach et al. (2021), Legrand and Bertrand (2019), Ma (2009), Othus et al. (2012), Peng and Taylor (2014), Peng and Yu (2021).

In a sample of data of the kind mentioned, we have observations on the time to an event of interest (we refer to them as “lifetimes”), possibly right-censored, of individuals from a population which contains some who are “susceptible” to suffering the event under consideration, and possibly also some who are “immune to”, “cured” of it, or are “longterm survivors”. For “susceptibles”, the issue is to infer properties of their lifetime distribution from the sample. For “immunes”, the main questions of interest are whether they are in fact present in the population, and if so in what proportion. Herein, we concentrate on the first question: based on the sample information, how confident can we be that immunes are in fact present in the population? Currently developed methods for assessing this ultimately rely in some way on the amount of follow-up in the sample.

We do not know whether a particular censored lifetime in the sample is from an immune or cured individual (uncensored lifetimes are obviously not from immunes); but, in aggregate, the presence of cured individuals may be signalled by an interval of constancy of the Kaplan-Meier estimator (Kaplan and Meier (1958) (KME)) at its right hand end; that is, the interval containing the censored lifetimes exceeding the largest uncensored lifetime. The length of that interval and the number of censored survival times larger than the largest uncensored survival time are important indicators for the presence of cured individuals, and for whether there is sufficient follow-up in the sample to be confident of their presence.

Ways of testing for sufficient follow-up are still in a very undeveloped state. One such test statistic, $Q_n$, is suggested in Maller and Zhou (1994) and Maller and Zhou (1996), p.81. Since then, there have been only two other definite
approaches that we know of, namely those of Shen (2000) (his statistic is denoted by $\tilde{\alpha}_n$) and Klebanov and Yakovlev (2007). We discuss these approaches further in Section 9, but otherwise restrict discussion and analysis to $Q_n$.

The joint distribution of the largest uncensored and the largest survival time in the sample is given in alternative ways in Maller and Resnick (2021) and Maller et al. (2022). In the present paper we apply the foundational results in Maller et al. (2022) to obtain exact finite sample as well as asymptotic distributions for $Q_n$, which can be used to assess whether follow-up is sufficient in a sample. The methods are illustrated with schematic and real data sets.

An important additional point is that statistics such as $Q_n$ and $\tilde{\alpha}_n$ can be used not only to test for sufficient follow-up but also to provide measures of how much follow-up there is in a sample. Both these aspects are prominent in a paper by Liu et al. (2018) where testing for and measurement of sufficient follow-up in the TCGA pan-cancer clinical data resource are done on a very extensive scale in order to provide recommendations to cancer researchers wishing to assess the adequacy of clinical follow-up in a medical situation. Liu et al. (2018) processed follow-up data files for 11,160 patients across 33 cancer types, calculating median follow-up times as well as median times to event (or censorship) based on the observed times for four endpoints (overall survival, disease-specific survival, disease-free interval, or progression-free interval). They used $Q_n$ and $\tilde{\alpha}_n$ to classify all $33 \times 4$ resulting KMEs as having sufficient or insufficient follow-up (or noted cases in which tests were inconclusive) in order to give endpoint usage recommendations for each cancer type. The analyses we present here help to validate the application of these tests in the data analysed in Liu et al. (2018).

2 Test Statistics for Sufficient follow-up

2.1 Notation and distributional setup

For the distributional results to follow we use the notation in Maller et al. (2022), which should be read in conjunction with the present paper. We assume a general independent censoring model ("the iid censoring model") with right censoring. A sample of size $n$ consists of observations on the sequence of iid (independent and identically distributed) 2-vectors $\{T_i = T_i^* \wedge U_i, C_i = 1(T_i^* \leq U_i); 1 \leq i \leq n\}$. The $T_i^*$ with continuous cumulative distribution
function (cdf) $F^*$ on $[0, \infty)$ represent the times of occurrence of an event under study, such as the death of a person, the onset of a disease, the recurrence of a disease, the arrest of a person charged with a crime, the re-arrest of an individual released from prison, etc. The $U_i$ with continuous cdf $G$ on $[0, \infty)$ are censoring random variables, independent of the $T_i^*$. In a sample of data from a population containing long-term survivors we observe the random variables $T_i = T_i^* \wedge U_i$, these being potential lifetimes censored at a limit of follow-up represented for individual $i$ by the random variable $U_i$. The random variables $C_i = 1(T_i^* \leq U_i)$ are censor indicators. Let $M(n) := \max_{1 \leq i \leq n} T_i$ be the largest observed survival time and let $M_u(n)$ be the largest observed uncensored survival time.

The censoring distribution $G$ of the $U_i$ is always assumed proper (total mass 1), but we allow the possibility that the distribution $F^*$ of the $T_i^*$ is improper. We assume $F^*$ to be of the form

$$F^*(t) = pF(t), \quad (2.1)$$

where $0 < p \leq 1$ and $F$ is a proper distribution. We think of $F$ as being the distribution of susceptible individuals in the population. Only susceptibles can experience the event of interest and have a potentially uncensored failure time. The remainder of the population is immune to the event of interest or cured of it. The presence of immunes is signalled by a value of $p < 1$, in which case the distribution $F^*$ is improper, with total mass $p$. Then $1 - p$ is the proportion of immune or cured individuals in the population. Observations on immunes are always censored; those on susceptibles may or may not be according as the corresponding $T_i^* > U_i$ or not.

Let $F^*(t) = 1 - F^*(t)$, $t \geq 0$, denote the survival function (tail function) of $F^*$, and similarly for $F$ and $G$. Let $\tau_{F^*} = \inf\{t > 0 : F^*(t) = 1\}$ (with the inf of the empty set equal to $\infty$) be the right extreme of the survival distribution $F^*$, and similarly $\tau_F$ and $\tau_G$ are the right extremes of $F$ and $G$. Let $H(t) := P(T_1 \leq t)$ be the distribution of the observed survival times $T_i = T_i^* \wedge U_i$, with tail $H(t) = 1 - H(t) = P(T_i^* \wedge U_i > t) = F^*(t)G(t)$, $t \geq 0$, and right extreme $\tau_H = \tau_{F^*} \wedge \tau_G$. We always have $H(\tau_H) = 1$, $G(\tau_G) = 1$ and $F(\tau_F) = 1$. When $p = 1$, so that $F^* \equiv F$, $F^*$ has total mass 1 and $\tau_{F^*} = \tau_F$; when $p < 1$ we have $\tau_{F^*} = \infty$, and $\tau_F \leq \tau_{F^*}$, with the possibility that $\tau_F < \tau_{F^*}$.
2.2 Test statistics and procedure

As test statistic for sufficient follow-up we focus on the statistic $Q_n$ proposed in [Maller and Zhou (1994)]. This is defined as follows. Consider a sample of size $n$ with all survival times necessarily in $[0, M(n)]$, a number $N_u(n)$ of uncensored survival times, necessarily in $[0, M_u(n)]$, a number $N_c^<(n)$ of censored survival times in $[0, M_u(n))$, and a number $N_c^>(n)$ of censored survival times in $(M_u(n), M(n)]$, thus with a total of $N_c(n) = N_c^<(n) + N_c^>(n) = n - N_u(n)$ censored survival times in the sample. Set $\Delta_n := 2M_u(n) - M(n)$. As in Maller and Zhou (1996), p.81 we define

$$Q_n = \frac{1}{n} \#\{\text{uncensored observations in } [\Delta_n, M_u(n))\}. \quad (2.2)$$

(Note that we exclude $M_u(n)$ itself when counting the number of uncensored observations greater than $\Delta_n$.) The statistic $Q_n$ is the proportion of uncensored observations in the interval $[2M_u(n) - M(n), M_u(n)]$, relative to the sample size $n$. It measures the length of the interval exceeding $M_u(n)$ but in a proportional rather than absolute way. A rationale for the definition (2.2) is given in Maller and Zhou (1996), p.84.

The distribution of $Q_n$ was unavailable when Maller and Zhou (1996) was written and had to be simulated to get quantiles. Our intention here is to get exact formulae (in Theorem 4.1 below) for the distribution of $Q_n$ under the iid censoring model. With these we can calculate asymptotic distributions (in Section 5) and percentage points when estimates of $F$ and $G$ are made from data (an example is in Section 8).

Our test procedure will be as follows. We have at hand survival data with hypothesized cured individuals present and wish to test for sufficient follow-up. This is specified in Maller and Zhou (1996), p.81, to be the parametric condition $\tau_F \leq \tau_G$. (For a rationale for this condition, see Sections 2.2 and 2.3 of Maller and Zhou (1996).) We proceed by assuming the contrapositive hypothesis, $H_0 : \tau_G < \tau_F$. If $H_0$ is true the probability of seeing a large value of the test statistic $Q_n$ is small. So we will reject $H_0$ and conclude that follow-up is sufficient if the observed value of the test statistic exceeds a nominated quantile of its distribution under $H_0$. A test based on large values of $Q_n$ will reject the hypothesis of insufficient follow-up with probability approaching 1 as sample size tends to infinity; this follows from the asymptotic results in Theorem 5.1. In order to understand the behaviour of $Q_n$, we first consider its
finite sample properties.

3 Understanding the sample properties of $Q_n$

The value of $Q_n$ depends in a complicated way on the numbers of censored and uncensored observations, the way they happen to occur below or above $M_u(n)$, and on the relative magnitudes of $M_u(n)$ and $M(n)$. In order to calculate its distribution under the iid censoring model we need to understand how it varies with these things. To do this we consider hypothetical sample situations, vary the mentioned quantities and see how the value of $Q_n$ changes.

We begin by considering possible values of $\Delta_n$. We always have $\Delta_n = 2M_u(n) - M(n) \leq 2M_u(n) - M_u(n) = M_u(n)$. Possible values of $\Delta_n$ range from $\Delta_n = -M(n)$ if $M_u(n) = 0$, equivalently, if all observations are censored, to $\Delta_n = M_u(n) = M(n)$ if $M_u(n) = M(n)$, equivalently, if the largest observation is uncensored. We have $\Delta_n = 0$ if it happens that $M_u(n) = M(n)/2$. Thus we may have $\Delta_n < 0$, $\Delta_n = 0$, or $\Delta_n > 0$. When $\Delta_n \leq 0$ then $[\Delta_n, M_u(n)) \supseteq [0, M_u(n))$ and (2.2) gives $nQ_n = N_u(n) - 1$. At the other extreme, the interval $[\Delta_n, M_u(n))$ may be empty, and this is certainly so when $\Delta_n = M_u(n)$. Whenever this occurs we set $Q_n = 0$.

Now think of the way $Q_n$ changes if we rearrange the conformation of the censored observations less than or greater than $M_u(n)$, by keeping $M(n)$ and $N_u(n) > 0$ fixed and varying $N_c^<(n)$ and $N_c^>(n)$. It helps to visualise the various situations with schematic KME diagrams in the different cases, as we show in Figures 1a – 1d.

We start with an extreme case.

Case 1: $N_c^<(n) = 0$, $N_c^>(n) > 0$ (see Fig. 1a). In this conformation all the censored observations in the sample form a level stretch of the KME between $M_u(n)$ and $M(n)$. In this case $M_u(n)$ takes the minimum possible value for the sample under this kind of rearrangement, $M(n) - M_u(n)$ takes the maximum possible value, $\Delta_n = 2M_u(n) - M(n) = M_u(n) - (M(n) - M_u(n))$ takes the minimum possible value, and $Q_n$ takes the maximum possible value under this kind of rearrangement for the sample. We reject $H_0 : \tau_G < \tau_F$ and conclude there is sufficient follow-up if we observe large values of $Q_n$, so this arrangement accords with our intuition that a (long) level stretch on the KME between $M_u(n)$ and $M(n)$ indicates there is sufficient follow-up.
Figure 1: Schematic KME diagrams
Case 2: $N_c^< (n) > 0$, $N_c^> (n) > 0$ (see Fig. 1b). As censored observations are moved to the left of $M_u(n)$, $M_u(n)$ tends to increase and $M(n) - M_u(n)$ tends to decrease (it cannot increase). So $\Delta_n$ will tend to increase and consequently $Q_n$ will tend to decrease. This accords with our intuition that a decrease in the number of censored observations above $M_u(n)$ and in the length of the level stretch of the KME between $M_u(n)$ and $M(n)$ makes it less likely to reject $H_0$, the hypothesis of insufficient follow-up.

Ultimately, continuing this process, we reach:

Case 3: $N_c^< (n) > 0$, $N_c^> (n) = 1$ (see Fig. 1c). The one censored observation above $M_u(n)$ is $M_u(n)$ itself and $\Delta_n = 2M_u(n) - M(n)$ will be close to or equal to $M_u(n)$. The interval $[\Delta_n, M_u(n))$ is small and $Q_n$ is small, possibly equal to 0 (this certainly occurs when $\Delta_n = M_u(n)$). This accords with our intuition that a short level stretch of the KME between $M_u(n)$ and $M(n)$ indicates via a small value of $Q_n$ that there is insufficient follow-up.

In these scenarios, $Q_n$ decreases monotonically from a sufficient follow-up situation to one with insufficient follow-up.

The actual values taken on by $Q_n$ in these scenarios depend on the relative magnitudes of $M_u(n)$ and $M(n)$. The possibilities are as follows. Note that since $N_u(n) > 0$, we have $M_u(n) > 0$.

(a) When $0 < M_u(n) \leq \frac{1}{2} M(n)$, then $\Delta_n \leq 0$ and $[\Delta_n, M_u(n)) \supseteq [0, M_u(n))$. In this case

$$Q_n = \frac{1}{n} \# \{\text{uncensored observations other than } M_u(n)\} = \frac{N_u(n) - 1}{n}.$$ 

This is the largest value $Q_n$ can take for a given sample.

(b) When $\frac{1}{2} M(n) < M_u(n) < M(n)$, then $\Delta_n > 0$ and the interval $[\Delta_n, M_u(n))$ contains, say, $k$ observations. We have $k \geq 0$ and $k \leq n - 1$ since there is at least one censored observation greater than $M_u(n)$, namely, $M(n)$. So we can write

$$Q_n = \frac{k}{n} = \frac{1}{n} \# \{\text{uncensored observations in } [\Delta_n, M_u(n))\}, \quad (3.1)$$

where $k$ decreases from its maximum value when $M_u(n)$ is near $\frac{1}{2} M(n)$, reaching 0 when $M_u(n)$ is near $M(n)$.

There are also two other extreme cases to consider.

(c) When $N_c^> (n) = 0$, then $M_u(n) = M(n)$, and the largest observation
is uncensored (see Fig. 1d). Then $\Delta_n = M_u(n)$, the interval $[\Delta_n, M_u(n))$ is empty, and $Q_n = 0$. Here the level stretch has length 0 and the low $Q_n$ value correctly reflects sufficient follow-up. (This case includes also the possibility that all observations are uncensored, corresponding to $N_u(n) = n$, and $k = n$.) But this Case (c) means there is no evidence of immunes and hence no issue of sufficient or insufficient follow-up. We condition on the non-occurrence of this event when calculating the distribution of $Q_n$.

(d) When $N_u(n) = 0$, all observations are censored, and, formally, $Q_n = 0$. This anomalous or ambiguous case is of no interest and we condition on its non-occurrence also, when calculating the distribution of $Q_n$.

![Figure 2: Possible Values for $Q_n$](image)

**Figure 2:** Possible Values for $Q_n$

### 4 Finite Sample Distribution of $Q_n$

Given the discussion in the previous section, in calculating the distribution of $Q_n$ we will eliminate the cases $M_u(n) = 0$ and $M_u(n) = M(n)$, and partition the event of interest, $\{0 < M_u(n) < M(n)\}$, as $\{0 < M_u(n) \leq \frac{1}{2} M(n)\} \cup \{\frac{1}{2} M(n) < M_u(n) < M(n)\}$. So we condition on $\{M_u(n) = t, M(n) = x\}$, where $0 < t < x \leq \tau_H$, and consider the cases $0 < t \leq \frac{1}{2} x$ and $\frac{1}{2} x < t < x$ separately.

Equivalently, we consider **Case A**: $2t - x \leq 0$, and **Case B**: $0 < 2t - x \leq \tau_H$, with $0 < t < x \leq \tau_H$ in both cases. Since we know the joint distribution of $M(n)$ and $M_u(n)$ from Theorem 2.3 of Maller et al. (2022), we can integrate to obtain the distribution of $Q_n$ conditional on $\{0 < M_u(n) < M(n)\}$. One such calculation is carried out in the proof of Theorem 4.1 and a large-sample version is in Theorem 5.1.
We set out some further preliminaries to Theorem 4.1. Recall the formula (3.1) for $Q_n$. Throughout we keep $n > 2$, $0 < t < x \leq \tau_H$ and $1 \leq r \leq n - 1$, and will begin by conditioning on the event $\{M_u(n) = t, M(n) = x, N^>_c(M_u(n)) = r\}$. We need some separate notation in Cases A and B. For Case A define

$$
\pi^A(t) := \frac{P(0 < T^*_1 \leq t, T^*_1 \leq U_1)}{P(T^*_1 \wedge U_1 \leq t)} = \int_0^t \frac{G(y) dF^*(y)}{H(t)}.
$$

(4.1)

(which does not depend on $x$) and for Case B define

$$
\pi^B(t, x) := \frac{P(2t - x < T^*_1 \leq t, T^*_1 \leq U_1)}{P(T^*_1 \wedge U_1 \leq t)} = \int_{2t-x}^t \frac{G(y) dF^*(y)}{H(t)}.
$$

(4.2)

Define also the probability

$$
p^>_c(t, x) = \frac{\int_{y=t}^x \frac{F^*(y) dG(y)}{H(t)}}{\int_{y=t}^x \frac{F^*(y) dG(y)}{H(t)} + H(t)},
$$

(4.3)

and let

$$
\rho^A(t, x) := (1 - p^>_c(t, x))\pi^A(t) \quad \text{and} \quad \rho^B(t, x) := (1 - p^>_c(t, x))\pi^B(t, x).
$$

(4.4)

Define integers $I^<_n := \{i \in \mathbb{N} : T_i < M_u(n)\}$ and let $\sigma^<$ be the smallest $\sigma$-field making $(T_i, C_i)_{i \in I^<_n}$ measurable. Likewise let $I^>_n := \{i \in \mathbb{N} : T_i > M_u(n)\}$ and let $\sigma^>$ be the smallest $\sigma$-field making $(T_i, C_i)_{i \in I^>_n}$ measurable. A key result from Theorem 2.1 and Corollary 5 of [Maller et al. (2022)] is that, conditional on the event $\{M_u(n) = t, M(n) = x, N^>_c(M_u(n)) = r\}$, or, equivalently, conditional on the event $\{M_u(n) = t, N^>_c(M_u(n)) = r\}$, the $\sigma$-fields $\sigma^<$ and $\sigma^>$ are independent, and the conditional probability of an event $A^<$ in $\sigma^<$ can be calculated by substituting truncated rvs $(T_i(t))$ having the distribution of $T_i$ given $T_i \leq t$ for the $(T_i)$ in $A^<$.

With this setup we can now state Lemma 4.1 (Proofs of the lemma and the subsequent Theorems 4.1 and 5.1 are in the supplementary material.)

**Lemma 4.1. Part (i):** We have for $1 \leq r \leq n - 1$, $0 < t < x \leq \tau_H$,

$$
P(N^>_c(M_u(n)) = r \mid M_u(n) = t, M(n) = x) = P(Bin(n - 2, p^>_c(t, x)) = r - 1).
$$

(4.5)
Part (ii): For $0 \leq k \leq n - 2$,

$$P(nQ_n = k | M_u(n) = t, M(n) = x) = P(Bin(n - 2, \rho(t, x)) = k), \quad (4.6)$$

where $\rho(t, x) = \rho^A(t, x)$ in Case A and $\rho(t, x) = \rho^B(t, x)$ in Case B (see (4.4)).

We need one more formula: by Eq. (2.14) of Maller et al. (2022) we have

$$P_n(dt, dx) := P(M_u(n) \in dt, M(n) \in dx) = n(n - 1) \left( \int_{y=t}^{x} F^*(y) dG(y) + H(t) \right)^{n-2} G(t) dF^*(t) F^*(x) dG(x). \quad (4.7)$$

Next we can state Theorem 4.1.

**Theorem 4.1.** Assume the iid censoring model in Subsection 2.1. Then for $n > 2$, $k = 0, 1, 2, \ldots, n - 2$,

$$P(nQ_n = k | 0 < M_u(n) < M(n)) = \frac{A_n(k) + B_n(k)}{D_n}, \quad (4.8)$$

where

$$A_n(k) = \int_{t=0}^{\tau/2} \int_{x=2t}^{\tau} P(Bin(n - 2, \rho^A(t, x)) = k) P_n(dt, dx) \quad (4.9)$$

and

$$B_n(k) = \left[ \int_{t=0}^{\tau/2} \int_{x=t}^{2t} + \int_{t=\tau/2}^{\tau} \int_{x=t}^{\tau} \right] P(Bin(n - 2, \rho^B(t, x)) = k) P_n(dt, dx) \quad (4.10)$$

(recall (4.7) for $P_n(dt, dx)$.) The denominator in (4.8) is

$$D_n = P(0 < M_u(n) < M(n)) = 1 - \left( \int_{t=0}^{\tau} F^*(z) dG(z) \right)^n \int_{t=0}^{\tau} H^{n-1}(t) G(t) dF^*(t). \quad (4.11)$$

**4.1 Probability mass functions of $Q_n$**

Figure 3 shows graphs of the probability mass functions (pmfs) of $nQ_n$ calculated from (4.8) for various scenarios with $F$ exponential, $G$ uniform, and $n = 50, 100, 150$. For small $n$ the pmfs are bimodal, reflecting the two components on the RHS of (4.8). The bimodality is least prominent when censoring
is heavy and disappears altogether as $n \to \infty$. The pmfs in Figure 3 are consistent with those obtained by simulation in Section 4.3 of Maller and Zhou (1996). The tables in Maller and Zhou (1996) are based on exponential survival distributions but remain relevant also for a certain scale family of distributions; see the Supplement for details.

![Figure 3: Probability mass functions for $nQ_n$. $F = \text{exp}(1)$, $p = 0.8$. Left column: $G = U[0,3]$; Right column: $G = U[0,6]$. Top, middle, bottom row: $n = 50, 100, 150$.](image)

We mentioned in connection with Liu et al. (2018) in Section 1 that $Q_n$ can be used not only to test for sufficient follow-up but also to provide a measure of how much follow-up there is in a sample. In this respect the bimodality evident in some of the pmfs in Figure 3 is an unsatisfactory feature but as we pointed out it disappears as $n \to \infty$ and samples of survival data are often of many thousands of individuals, as is the case in Liu et al. (2018).

We go on to give the asymptotic distribution of $Q_n$ in the next section.
5 Asymptotic Distribution of $Q_n$

In this section we give the large sample distribution of $Q_n$ in situations both of insufficient (the main case of interest) and sufficient follow-up. We assume $G$ has a finite right endpoint $\tau_G$ and $\overline{G}$ behaves linearly near $\tau_G$. We also impose mild regularity conditions on $F$. These conditions are satisfied when $G$ is uniform on $[0, \tau_G]$ and $F$ is exponential, for example. The asymptotic distribution of $Q_n$ is shown to be geometric when $\tau_G < \tau_F$ and normal when $\tau_F < \tau_G$, under these conditions. Our main result for this section is:

**Theorem 5.1.** [Asymptotic distribution of $Q_n$] Assume the iid censoring model and $0 < p \leq 1$ throughout. We have the following limiting distributions in cases of interest.

**Case 1:** Assume $\tau_G < \tau_F \leq \infty$, so $\tau_H = \tau_G < \infty$. Suppose also

$$\overline{G}(\tau_G - z) = a_G(1 + o(1))z \text{ as } z \downarrow 0,$$

for a constant $a_G > 0$, and, in addition, $F$ has a density in a neighbourhood of $\tau_G$ which is positive and continuous at $\tau_G$. Then

$$\lim_{n \to \infty} P(nQ_n = k) = \frac{1}{4} \left(\frac{3}{4}\right)^k, \quad k = 0, 1, 2, \ldots,$$

so $nQ_n$ is asymptotically geometric with parameter $1/4$.

**Case 2:** Assume $\tau_F < \tau_G < 2\tau_F$, so that $\tau_H = \tau_F < \infty$. Suppose also that 

$$\overline{G}(\tau_G - z) = a_G(1 + o(1))z,$$

holds and in addition

$$\overline{F}(\tau_F - z) = a_F(1 + o(1))z,$$

for a constant $a_F > 0$. Then as $n \to \infty$

$$\frac{\sqrt{n}(Q_n - \nu_B)}{\sqrt{\nu_B(1 - \nu_B)}} \xrightarrow{D} N(0, 1),$$

where the parameter $\nu_B = p \int_{2\tau_F - \tau_G}^{\tau_F} \overline{G}(y) \, dF(y) / (1 - p\overline{G}(\tau_F)) \in (0, 1)$.

**Case 3:** Assume $2\tau_F < \tau_G < \infty$, so that $\tau_H = \tau_F < \infty$. Suppose also that 

$$\overline{G}(\tau_G - z) = a_G(1 + o(1))z,$$

and 

$$\overline{F}(\tau_F - z) = a_F(1 + o(1))z,$$

hold. Then as $n \to \infty$

$$\frac{\sqrt{n}(Q_n - \nu_A)}{\sqrt{\nu_A(1 - \nu_A)}} \xrightarrow{D} N(0, 1),$$
where $\nu^A = p \int_0^\tau \overline{G}(y) dF(y)/(1 - pG(\tau_F))$.

**Remarks.** (i) Case 1 with $\tau_G < \tau_F$ is a situation of insufficient follow-up, and in it $nQ_n$ has asymptotically a finite nondegenerate limit (a geometric rv). Hence in this situation $Q_n \xrightarrow{p} 0$ as $n \to \infty$, showing that the hypothesis of insufficient follow-up will be accepted in large samples (with probability approaching 1 as $n \to \infty$) when it is true. When follow-up is sufficient, i.e, Cases 2 and 3, $Q_n$ is ultimately normally distributed around positive levels $\nu^A$ or $\nu^B$ in large samples, and, depending on sample size, the hypothesis of insufficient follow-up will be rejected, as it should be. The specific formulae for the distributions in (5.2), (5.4) and (5.5), enable the power calculations presented in the next section.

(ii) We remark that conditions (5.1) and (5.3) are special cases of those imposed in Theorem 3.1 of Maller et al. (2022), where more generally, a regularly varying function is allowed in place of the linear factors in (5.1) and (5.3). However our present result is general enough for wide applicability.

# 6 Power of the $Q_n$ Test

In this section we use the asymptotic distributions of $Q_n$ found under the assumptions (5.1) and the density condition on $F$ in Section 5, to calculate the power of the $Q_n$ test as the parameter $\tau_G$, reflecting the amount of follow-up, changes. In view of (5.2), it is more convenient to use $nQ_n$ than $Q_n$.

We proceed by calculating the 95-th quantile $K_{0.95}$ of the asymptotic distribution of $nQ_n$ from (5.2), assuming the hypothesis $H_0 : \tau_G < \tau_F$ (insufficient follow-up) is true. From (5.2) we can find $K_{0.95}$ explicitly as

$$K_{0.95} = K_{0.95}(p, \tau_G) = \frac{\log(0.05)}{\log(3/4)} - 1 = 9.41.$$  \hfill (6.1)

Thus, under $H_0$, we have $P(nQ_n > K_{0.95}) \approx 0.05$, for large $n$. Then we successively increase $\tau_G$ above $\tau_F$, hence in the region of the alternate hypothesis, and use (5.4) and (5.5) to calculate the corresponding values of $P(nQ_n > K_{0.95})$. Thus when $\tau_F < \tau_G < 2\tau_F$, according to (5.4) we set

$$P(nQ_n > K_{0.95}) = P \left( \frac{nQ_n - n\nu^B}{\sqrt{n\nu^B(1 - \nu^B)}} > \frac{K_{0.95} - n\nu^B}{\sqrt{n\nu^B(1 - \nu^B)}} \right).$$
\[
\approx P \left( N(0,1) > \frac{K_{0.95} - n\nu^B}{\sqrt{n\nu^B(1 - \nu^B)}} \right), \tag{6.2}
\]

where \( \nu^B = p \int_{2\tau_F - \tau_G}^{\tau_G} G(y) \, dF(y)/(1 - pG(\tau_F)); \) and when \( 2\tau_F < \tau_G, \) according to (5.5) we replace \( \nu^B \) in (6.2) by \( \nu^A = p \int_{0}^{\tau_F} G(y) \, dF(y)/(1 - pG(\tau_F)). \)

Using \( \nu \) to denote \( \nu^A \) or \( \nu^B \) as appropriate, we will use the approximation (6.2) only when \( n\nu \) is large, and take the function of \( \tau_G \) defined by

\[
P(\tau_G; \nu) := P \left( N(0,1) > \min \left( \frac{K_{0.95} - n\nu}{\sqrt{n\nu(1 - \nu)}}, 1.58 \right) \right), \tag{6.3}
\]

as an approximation to the power of the test. Keep \( \tau_G > \tau_F, \) and, at first, \( \tau_F < \tau_G < 2\tau_F. \) As \( \tau_G \) increases above \( \tau_F, \) \( \nu^B \) increases and \( P(\tau_G; \nu^B) \) increases.

(Notice that \( K_{0.95} \) no longer depends on \( \tau_G \) for values of \( \tau_G > \tau_F. \)) When \( \nu^B = K_{0.95}/n \) then \( P(\tau_G; \nu^B) \) reaches 0.50, and once \( \tau_G \) reaches \( 2\tau_F \) then \( \nu^B = p \int_{0}^{\tau_F} G(y) \, dF(y)/(1 - pG(\tau_F)). \) For \( \tau_G \) values greater than this \( \nu^B \) is replaced in (6.3) by \( \nu^A = p \int_{0}^{\tau_F} G(y) \, dF(y)/(1 - pG(\tau_F)) \) and we note that \( \nu^A = \nu^B \) at the transition. For larger values of \( \tau_G, \) \( P(\tau_G; \nu^A) \) stays constant at a value which approaches 1 as \( n \to \infty. \)

In summary, the power function of the test appears to behave very well. We assume for illustration a sample size of \( n = 100, \) for \( G \) a Uniform\([0, \tau_G]\) distribution, and for \( F \) a unit exponential distribution truncated at a finite value \( \tau_F = 5. \) Since the probability in the tail of \( F \) above 5 is less than 0.01, this is effectively assuming a unit exponential distribution for susceptible lifetimes. A graph of \( P(\tau_G; \nu) \) for these parameter values is in Fig. 4.

![Graph](image)

Figure 4: Power as a function of \( \tau_G \) for \( Q_n, \) with \( F \sim \exp(1), \) truncated at \( \tau_F = 5; G \sim [0, \tau_G]; n = 100. \)
7 Dependent Censoring

The distributional results derived so far have been based on the assumption of independence between the times of occurrence of the event under study and the censoring mechanism. This assumption may not be tenable in some situations and there have been a number of studies where it has been relaxed. See for example the competing dependent risks of leukaemia relapse and graft versus host disease analysed in Kalbfleisch and Prentice (2003) and Kovar et al. (2018). In order to assess the robustness of our results to departures from independence we consider the distribution of $Q_n$ in a model where there is dependence between the survival and censoring distributions.

We assume a sample consists of observations on the 2-vectors

$$ (T_i = T_i^* \land U_i, \ C_i = 1(T_i^* \leq U_i); \ 1 \leq i \leq n), $$

where now the $T_i^*$ and $C_i$ are dependent with a joint continuous distribution $H$ having marginal distributions $F^*$ and $G$ on $[0, \infty)$. We model the dependence between $F^*$ and $G$ using a copula to connect the marginal distributions with the joint distribution.

Numerous copulas are defined and described in Nelsen (2006), to which we refer for background. For our bivariate setup we have 2 uniform random variables $W_1, W_2$, whose joint distribution function is specified as

$$ J(w_1, w_2, \theta) := P(W_1 \leq w_1, W_2 \leq w_2), \quad (7.1) $$

for a copula parameter $\theta$ which quantifies the dependence between $W_1$ and $W_2$. We restrict our discussion to the class of Archimedean copulas which contains many subfamilies capable of representing different dependency structures. The distribution function of an Archimedean copula is written as:

$$ J(w_1, w_2) = \Phi^{-1}(\Phi(w_1) + \Phi(w_2)), \ 0 \leq w_1, w_2 \leq 1, \quad (7.2) $$

where the function $\Phi$ is the generator function of the copula.

We consider two generators which give rise to two Archimedean copulas: the Frank and Ali-Mikhail-Haq (AMH) copulas. Each copula has an analytical expression that links its parameters to its related Kendall $\tau$ as a measure of association (Salvadori et al. (2007)).
The Frank copula (Frank (1979)) has generator
\[ \Phi(t) = -\log\frac{e^{-\theta t} - 1}{e^{-\theta} - 1}, \quad \theta \in \mathbb{R} \setminus \{0\}, \]
giving rise to the copula function
\[ J_{\text{Frank}}(w_1, w_2) = -\frac{1}{\theta} \log \left( 1 + \frac{(e^{-\theta w_1} - 1)(e^{-\theta w_2} - 1)}{e^{-\theta} - 1} \right). \]

The Ali-Mikhail-Haq copula (Ali et al. (1978)) has generator
\[ \Phi(t) = \log \left( \frac{1}{1 - \theta(1-t)} \right), \quad \theta \in [-1, 1], \]
giving rise to the copula function
\[ C_{\text{AMH}}(w_1, w_2) = \frac{w_1 w_2}{1 - \theta(1-w_1)(1-w_2)}. \]

We proceed by assuming that \( H \) is a bivariate distribution with specified continuous marginals \( F^* \) and \( G \). By virtue of Sklar’s theorem (Sklar (1959)), \( H \) can be expressed in a unique way via a 2-copula \( J \). In order to simulate an observation on \( (T^*_i, U_i) \sim H \), it is sufficient to simulate a vector \( (W_1, W_2) \sim J \) with values \( w_1 \) and \( w_2 \) where the r.v.’s \( W_1 \) and \( W_2 \) are uniform on \([0, 1]\). Then
\[ t^* = F_{\star \leftarrow}^*(w_1), \quad u = G_{\star \leftarrow}(w_2), \]
is an observation on \((T^*, U)\) having the required joint distribution. (see Salvadori et al. (2007), Appendix A).

For our robustness analysis we simulated samples of size \( n = 50, 100, 150 \), from a \( J \) based on the Frank and AMH copulas for various values of \( \theta \). We took \( F^* = pF \), where \( F \) is exponential with parameter 1, \( G = U[0, 6] \) and \( p = 0.8 \). In each sample we calculated the value of \( Q_n \) and repeated this \( N = 10000 \) times to draw up the pmfs of \( Q_n \) (Figures 5 and 6). In each figure the pmf for \( \theta = 0 \) corresponds to independence. Viewing from the centre panel left we see that introducing negative dependence tends to concentrate the mass near small values of \( Q_n \); viewing from the centre panel right shows that positive dependence tends shifts the pmfs closer to normal. Percentage points calculated from these distributions could be used for correction if dependence...
Figure 5: Probability mass functions for $nQ_n$ with Frank copula for dependence. $F = \exp(1)$, $p = 0.8$, $G = U[0, 6]$. Top, middle, bottom panel: $n = 50, 100, 150$. Left to right: $\theta = 300, 6, 0, -6, -300$.

is assumed or detected in a sample.

## 8 Data Example

We calculated KMEs for the survival and censoring distributions from data for glioma (brain cancer) patients contained in the SEER (2019) database (Figures 7a and 7b). This is observational rather than from a randomised clinical trial but we use it here just to illustrate how consideration of followup with the $Q_n$ test can add value to an analysis of censored survival data.

The data was subdivided into two classes: Type 9380 (4248 patient records, of which 2075 are censored) and Other Types\(^{1}\) (54375 patient records, 20482 censored) according to the SEER classification scheme.

The maximum values of the KMEs are 0.68 for Type 9380 and 0.80 for

\(^{1}\)Types 9381, 9382, 9383, 9384, 9392, 9401, 9430, 9451, 9440, 9441, 9442, as used in Yang et al. (2018).
Figure 6: Probability mass functions for $nQ_n$ with AMH copula for dependence. $F = \exp(1)$, $p = 0.8$, $G = U[0,6]$. Top, middle, bottom panel: $n = 50, 100, 150$. Left to right: $\theta = 1, 0.5, 0, -0.5, -1$.

Other Types, suggesting cured probabilities of 0.32 for Type 9380 and 0.20 for Other Types. These are significantly different from 0 based on Greenwood’s formula for the variance of the KME, or using the tables in Maller and Zhou (1996). But is followup sufficient for us to be confident in concluding cured components? For Type 9380 we note a level stretch at the end of the KME at 503 months, with the largest uncensored observation at 435 months. Measuring back $503 - 435 = 68$ months we come to 367 months, and the number of uncensored observations in $[367, 435)$ is found to be 3. So $nQ_n = 3$ for this data. Since the sample size is large we can use Case 1 of Theorem 5.1 to calculate the p-value of the statistic for testing $H_0 : \tau_G < \tau_F$ as $(3/4)^3 = 0.42$ which is far from significance. So we do not reject $H_0$ and decide that followup is insufficient for this data. The same conclusion follows using the tables in Maller and Zhou (1996). We can see that, despite apparent levellings in Figure 7a, the curves continue to rise, with late deaths still occurring up till 400 months after diagnosis.

This test is nonparametric. But having failed to reject $H_0 : \tau_G < \tau_F$, Cases 2 and 3 of Theorem 5.1 become relevant, and we can also consider the pos-
(a) Survival KMEs for Glioma Types with fitted generalised gamma distributions.

(b) Censor KMEs for Glioma Types with fitted generalised gamma distributions.

The possibility that $\tau_G = \tau_F = \infty$. The latter case is not included in Theorem 5.1 as the corresponding result requires assumptions on the asymptotic behaviour of $(M_u(n), M(n))$, but it can be shown that $Q_n$ is asymptotically normal under reasonable assumptions. In order to apply Theorem 5.1, estimates of the distributions of $F$ and $G$ are needed. Generalised gamma distributions with a cured component as discussed in Jackson (2016) and Amdahl (2020) fit the data quite well (Figures 7a and 7b) and can be used for further analysis. Knowledge of the exact distribution allows for simulation via MCMC, for example.

For the Other glioma types the value of $nQ_n$ is 13 and the p-value using Case 1 of Theorem 5.1 is 0.02. For this data we reject $H_0 : \tau_G < \tau_F$ and decide that followup is sufficient. There is only a small level stretch at the end of the KME, but the conformation of censored and uncensored observations mean that it is significant. Further details of the data and analysis are in the Supplement.

This brief discussion is not meant to be a substantial analysis of this data, at all, but it highlights the valuable information present in the observations at the right hand end of a KME, and how the $Q_n$ statistic can guide us in interpreting it.

\cite{Lopez-Cheda2021} for alternative nonparametric fitting.
9 Discussion

Calculation of exact distributions (under the iid censoring model) makes unnecessary the need for simulations of percentage points, though in practice the unknown distributions must be estimated or postulated. This includes making assumptions about their right hand endpoints, and, especially, whether they are finite or not.

Most practical is to assume \( \tau_G < \infty \) since observation must always cease at some finite point. In many cases the assumption \( \tau_F < \infty \) may also be natural. Certainly in real survival data no individual lives forever, but we would have \( \tau_F = \infty \) for example when studying the occurrence of an infectious disease where an immune individual would never contract the disease no matter how long the follow-up. (For just such an analysis with children immune to malaria, see Cairns et al. (2013).) Regardless of the situation, in modelling exercises it is not uncommon to use an exponential, Weibull, lognormal, or Gumbel, with infinite right endpoints, as the lifetime distribution. In doing so we accept that the probability of seeing an extremely long lifetime under the assumed model is negligible, so the theoretical approximation is good enough for practical purposes.

It is natural to base tests for sufficient follow-up on the length of the interval \( (M_u(n), M(n)] \), or the number of censored survival times larger than the largest uncensored survival time, or some combination or variant of these. Kaplan-Meier plots provide very strong intuition in this respect; see for example the very evocative plots in Powles et al. (2021), who are expressly concerned with “determin(ing) which patients ... are cured after surgery.”

As other test statistics we might use the difference between the extremes, \( M(n) - M_u(n) \), or a standardised version of this such as \( R_n = 1 - M_u(n)/M(n) \), which is in \( (0, 1) \). Formulae for their distributions are in Maller et al. (2022). These variables measure the absolute or relative length of the level stretch of the KME rather than a proportion of observations related to them, as \( Q_n \) does. At present their properties remain to be investigated in detail. We note that they, like \( Q_n \), are very sensitive to the occurrence of one or a few failures in the righthand end of the KME. This is a robustness issue such as has to be addressed in any statistical analysis. A test for outliers in the iid model is in Maller and Zhou (1994). The Shen (2000) statistic \( \tilde{\alpha}_n \) is suggested by similar arguments to the way \( Q_n \) was obtained in Maller and Zhou (1996).
though the rationale seems not so obvious and the sample properties not so clear as for $Q_n$. Shen (2000) does not give a formula for the distribution of $\tilde{\alpha}_n$. We expect that one could be obtained as a modification of the way we calculated the distribution of $Q_n$ in Theorem 4.1, but the computations are more difficult. Shen reports, based on some limited simulations, that $\tilde{\alpha}_n$ sometimes performed better than $Q_n$ in terms of Type 1 error and power. A more extensive investigation of this is warranted.

Klebanov and Yakovlev (2007) give a succinct overview of the $Q_n$ statistic as presented in Maller and Zhou (1996) and discuss some of its properties. They draw attention to a perceived deficiency of the statistic, as follows. Suppose follow-up in a sample were hypothetically extended beyond what’s currently there. It’s possible then that a long-lived susceptible individual with currently censored lifetime may die during the extended follow-up period, and that the $Q_n$ value calculated on the extended sample then decreases from its former value, possibly even to 0. Klebanov and Yakovlev see this non-monotone behavior as problematic. But there is really no contradiction here. On the extended sample, with its late failure, the new, low, $Q_n$ is correctly registering that there is insufficient follow-up. If in this hypothetical situation we continue to increase follow-up, susceptible individuals will continue to die (all do, eventually), while those who are immune will remain so, and with extended follow-up. The $Q_n$ value may well fluctuate, but eventually only cured individuals will be left and the continued follow-up will give rise to increasing values of $Q_n$, till it reaches its maximum value for the sample. At each stage $Q_n$ is correctly (according to its constitution) indicating the extent of follow-up. There is no reason why $Q_n$ should be monotone in a hypothetical situation of increasing follow-up.

Nevertheless the quite different approach in Klebanov and Yakovlev (2007) provides a potentially useful perspective on the problem. Unfortunately however their proposed statistic is technically complex and very non-intuitive and its application would likely be restricted to specialist statisticians, whereas an approach based on the length of the level stretch at the end of the KME is highly visible and interpretable, and easily understood by practitioners. Shen’s statistic is also constructed in this way. That there is a need and a desire for a summary statistic with these properties is well exemplified by the Liu et al. (2018) analysis.

Understanding how $Q_n$ depends on sample properties of censored data,
and the formulae for the exact and asymptotic distributions of $Q_n$ we have obtained, open the way to its more general use in the analysis of survival data with immune or cured individuals. We note that under $H_0: \tau_G < \tau_F$, the hypothesis of insufficient follow-up, with some reasonable side conditions, the asymptotic distribution of $Q_n$ is completely non-parametric (cf. (5.2)). Future directions of research could usefully include issues of sufficient follow-up in competing risks analysis, and in multivariate survival analysis with cured individuals. For the latter, see Chatterjee and Shih (2001), Chatterjee and Shih (2003) and Coelho-Barros et al. (2016).

Shen (2000) and Klebanov and Yakovlev (2007) quote Maller and Zhou (1996) to the effect that $Q_n$ is by no means the last word on the subject, and this is worth stressing again here. Having formulae for the exact and asymptotic distributions of $Q_n$ in the iid censoring model is a big step forward, but there is much still to be explored in the analysis of sufficient follow-up and cure models in general.

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