COMMENTARY

Reverse survivor bias in observational studies involving cohorts: a lesson from '1:1' trauma studies

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Survivor (immortal time) bias has been extensively covered in the literature.[1-5] It occurs in observational studies when there is a time gap between when tallying of mortality begins and when treatment becomes available to some patients.[1] By design, all deaths occurring during this time gap are categorised as belonging to the non-treatment group, and only survivors of this initial time gap are potentially exposed to treatment, thus skewing the data in favour of treatment.[2] Essentially, some patients die not because they do not receive the treatment, they do not receive the treatment because they die.[3] To eliminate this bias, one apparently intuitive solution is to exclude from the analysis all deaths during the time gap. However, since it is the sickest patients who die the earliest, the surviving cohort is less likely to demonstrate the full benefits of any potentially effective treatment being studied.[4] Had the treatment been immediately available and given, the greatest benefit could very well be evident in these sickest patients. This 'reverse survivor bias' against a potentially effective treatment has received very little coverage in the literature. We shall discuss this bias in connection with studies on massive haemorrhage.

Survivor and reverse survivor biases in '1:1' observational studies

Patients admitted with massive haemorrhage after trauma are given erythrocytes immediately. Fresh frozen plasma (FFP) transfusion is typically given hours later.

The FFP:erythrocyte treatment ratio starts from zero but increases over time, such that at some point, it reaches '1:1' in some surviving patients. Whereas some surviving patients may receive '1:1', those who die early (before '1:1' becomes available), together with those who die after the immortal time period (ie after '1:1' becomes available) and for whatever reason do not receive '1:1' treatment are categorised in the non-'1:1' cohort. The 24-hour survival rate is thus likely to be higher in the '1:1' cohort. This survivor bias is observed in many '1:1' studies.[1-5]

Let us see how excluding deaths during the immortal time period may create a reverse survivor bias. Consider a hypothetical '1:1' study in which the clinical course is divided into 24 intervals. For each interval, a proportion of patients (d) die. We assume four intervals will pass during which unavailability of enough FFP prevents the ratio from reaching '1:1'. We herein assume that on average by the 5th interval, some patients will have received enough FFP to reach a '1:1' ratio, and so we start at the 5th time interval categorising patients to '1:1' or non-'1:1' cohorts. We shall assume that once a patient enters the '1:1' cohort, his cumulative FFP–to–packed red blood cell ratio stays at approximately 1:1 till the end of the 24th interval.[3,6]

We divide those who die into:

1. *DWI* (Dead while Waiting for Intervention): the number of patients dead within the first four intervals.
2. *DHI* (Dead and Had Intervention): the number of patients dead any time after the first four intervals and who had "1:1".
3. *DNoI* (Dead with No Intervention): the number of patients dead any time after the first four intervals and who had the chance to receive "1:1", but did not.

Let the probability of dying during the 1st interval be d_1, the 2nd interval be d_2, etc. The probability of surviving the first four intervals is $(1-d_1)(1-d_2)(1-d_3)(1-d_4)$, and of dying sometime during these intervals, $1-[(1-d_1)(1-d_2)(1-d_3)(1-d_4)]$.

In military trauma, most potentially salvageable patients die from haemorrhage and most deaths occur within 1 to 2 hours.[7] In civilian trauma, haemorrhage is the most important cause of death in the early phase with 60% of such deaths occurring within 3 hours of admission.[6] Furthermore, massively transfused patients who survive long enough for intensive care unit admission have significantly better haemodynamics and less acidosis on admission than those who do not.[8] Hence we might reasonably assume declining probability of death after admission as an illustration such that d_1=0.15, d_2=0.13, d_3=0.11, d_4=0.09, and a cohort at time 0 of 100 patients. The probability of death during the first four time intervals is $1-(1-d_1)(1-d_2)(1-d_3)(1-d_4) = 0.4$, and the number of deaths is $100\times0.4 = 40$.

After the first four time intervals, the 60 survivors are split equally between '1:1' and non-'1:1'. The chance of a patient dying during the remaining 20 intervals is $1-(1-d_5)(1-d_6)(1-d_7)(1-d_8)\ldots(1-d_{24})$. Assuming d_5–d_{24} stabilise to 0.025, $1-(1-d_5)(1-d_6)(1-d_7)(1-d_8)\ldots(1-d_{24})$ becomes $1-(1-0.025)^{20} = 0.4$. Since there are 30

patients who made it to the 5th interval and are in the non-intervention group, *DNoI* is $30[1-(1-0.025)^{20}] = 12$.

Next, we calculate *DHI*. We define the risk reduction factor of the intervention as *r*, which has a value between 0 (100% effective) and 1 (completely useless). The risk of dying in any interval '*i*' becomes $r_i d_i$. Then $DHI = 30[1-(1-r_5d_5)(1-r_6d_6)(1-r_7d_7)(1-r_8d_8)\ldots(1-r_{24}d_{24})]$.

To demonstrate survivor bias, assume that the intervention in our study is a placebo (all r_i=1). So in our formula for *DHI*, all $r_i d_i$ become d_i. Thus $DHI = 30[1-(1-0.025)^{20}] = DNoI$. We now calculate relative risk (RR) of the intervention. For the '1:1' group, 30 patients had '1:1' and there are 12 deaths, so the death rate is 12/30 = 0.4. For the non-'1:1' group, there were the 40 who died during the first four intervals plus the 12 who died and did not receive '1:1' between intervals 5 and 24, producing a death rate of (40+12)/(40+30) = 0.74. The RR of intervention is = 0.4/0.74 = 0.54. And thus we have a placebo, but the study shows RR = 0.54. Indeed, studies of such design have shown impressive RRs associated with '1:1'.[5]

Can we eliminate this bias by discarding group *DWI* and analysing only patients who survived the first four intervals? Since the death rate in both the intervention and non-intervention groups is 12/30, RR for '1:1' is 1. It seems that the answer is yes, but only if the intervention is useless.

We will now examine reverse survivor bias. This can occur where you have a high death rate at the beginning of the study and an effective treatment from which the sickest patients benefit the most and where benefits derived by less-sick patients are less.

Consider again massive traumatic haemorrhage in which the initial death rate is high, in large part due to coagulopathy.[9,10] Hence FFP therapy, if effective, is likely to be so during the early phase. After a patient has been stabilised, additional FFP is unlikely to be of high value.

These considerations suggest that the therapeutic effect *r* may be higher during the initial intervals. Arbitrarily, we set $r_1 = 0.3$, $r_2 = 0.4$, $r_3 = 0.5$, $r_4 = 0.6$ and r_5-r_{24} at 0.7. If we simulate a randomised control trial (RCT) by applying '1:1' at time 0 to half the cohort, the risk of death in the non-intervention group is $1-[(1-d_1)(1-d_2)(1-d_3)(1-d_4)\ldots(1-d_{24})]$ and in the intervention group is $1-[(1-r_1d_1)(1-r_2d_2)(1-r_3d_3)(1-r_4d_4)\ldots(1-r_{24}d_{24})]$. The RR of '1:1' thus calculated is 0.68. This is the 'true' effect of the treatment. However, if '1:1' is unavailable until the 5th interval, and we compare the intervention and non-intervention groups without excluding deaths during the first four intervals, RR for "1:1" becomes (9/30)/[(40+12)/(40+30)] = 0.404 (benefits overestimated due to survivor bias). If we exclude patients who died during the first four intervals, the RR for '1:1' becomes (9/30)/(12/30) = 0.75 (benefits underestimated due to reverse survivor bias).

Getting around both types of survivor biases—the importance of early data

We therefore have a conundrum: if '1:1' were effective, the presence of survivor bias when early deaths are included casts doubt on the results, but excluding early deaths dilutes any positive results because of reverse survivor bias.

To circumvent these problems, one may treat the intervention as a time-dependent covariate,[3,6] or compare patients after institution of a '1:1' protocol against a historical cohort.[5,10,11] However, all these exercises are of value only if we have data from those first hours after trauma. As centres are making thawed plasma immediately available to trauma patients, studies such as PROMMTT[6,10,11] will possibly shed new light on this controversy.

Other confounders include the tendency that during resuscitation, patients with more severe bleeding tend to be given more FFP, skewing the results against higher FFP use in observational '1:1' studies. The much anticipated RCTs[12-14] currently underway will eliminate most confounders that plague uncontrolled studies. To be valuable, however, RCTs must include crucial early data, without which even they would be at risk of reverse survivor bias.

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Answers to CME Programme
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I. Impact of magnetic resonance imaging on preoperative planning for breast cancer surgery

A	1. False	2. True	3. True	4. False	5. True
B	1. True	2. False	3. False	4. True	5. True

Hong Kong Med J 2013;19:300–4

II. Clinical profile of patients with undiagnosed human immunodeficiency virus infection presenting to a local emergency department: a pilot study

A	1. True	2. False	3. False	4. True	5. True
B	1. False	2. True	3. False	4. True	5. False