Systematic review of actual 10-year survival following resection for hepatocellular carcinoma

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Abstract

Background: Hepatic resection is a potentially curative therapy for hepatocellular carcinoma (HCC), but recurrence of disease is very common. Few studies have reported 10-year actual survival rates following hepatic resection; instead, most have used actuarial measures based on the Kaplan–Meier method. This systematic review aims to document 10-year actual survival rates and to identify factors significant in determining prognosis.

Methods: A comprehensive search was undertaken of MEDLINE and EMBASE. Only studies reporting the absolute number of patients alive at 10 years after first resection for HCC were included; these figures were used to calculate the actual 10-year survival rate. A qualitative review and analysis of the prognostic factors identified in the included studies were performed.

Results: Fourteen studies, all of which were retrospective case series, including data on 4197 patients with HCC were analysed. Ten years following resection, 303 of these patients were alive. The 10-year actual survival rate was 7.2%, whereas the actuarial survival quoted from the same studies was 26.8%. Positive prognostic factors included better hepatic function, a wider surgical margin and the absence of satellite lesions.

Conclusions: The actual long-term survival rate after resection of HCC is significantly inferior to reported actuarial survival rates. The Kaplan–Meier method of actuarial survival analysis tends to overestimate survival outcomes as a result of censorship of data and subgroup analysis.

Keywords
hepatocellular carcinoma, primary liver tumour, hepatectomy, liver resection, survival, systematic review

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cause of cancer worldwide and is the fourth leading cause of cancer-related death.1 The incidence and prevalence of HCC are highest in Southeast Asia and West Africa, but are rising in developed countries.1 Both surgical resection and liver transplantation are potentially curative treatments for resectable HCC,2 although 95% of HCC patients in Western populations have coexistent cirrhosis of the liver.3 Even for small and resectable HCC, transplantation is the preferred treatment option as it addresses both the apparent tumour and tumours that are not yet apparent, and the underlying cirrhosis.4 However, its usage is limited by the lack of donor organs.5

Although it has been recommended that direct clinical outcomes such as overall actual survival should be used as an endpoint in studies of HCC,6 actuarial survival measures remain the most often reported. The Kaplan–Meier method of actuarial survival analysis was first published in the 1950s as a way of estimating outcomes with incomplete data.7 The major risk for bias associated with this method is a result of the process of censoring, whereby certain patients are excluded from the final analysis.8 The reasons for exclusion may include loss to follow-up, perioperative
mortality or death from other causes. The Kaplan–Meier method also allows subset analysis to be used and then applied to the group as a whole. When applied to survival data, these approaches can lead to a gross overestimation of survival, which is misleading for both clinicians and patients.

The primary purpose of this study was to estimate, by a systematic review of published data, actual 10-year survival following resection of HCC. The secondary aim was to establish prognostic factors associated with improved survival.

**Materials and methods**

**Literature search**

A comprehensive search of the MEDLINE and EMBASE databases was undertaken in the first week of November 2011. The search strategy is provided in Appendix A1. A manual search of the references of the retrieved studies was performed. In the case of duplicate reporting of the same study population, the report that included the largest amount of outcome data was included.

**Inclusion and exclusion criteria**

Studies were included if they examined 10-year survival following resection of HCC in adults and quoted an actual number or percentage of survivors, or included sufficient data for these to be determined. Studies were excluded if they reported data for fewer than five patients, if 10-year follow-up was not complete, or if the data had been previously published, or the information reported was insufficient to calculate a 10-year actual survival.

**Outcome measures**

In order to determine the primary outcome measure of 10-year survival, the total number of patients alive at 10 years was divided by the total number of patients included in the study. The secondary outcome measures sought in each study were the prognostic factors associated with survival. Because of the heterogeneity of the data reported in each study, formal meta-regression was not feasible. In each study, the factors reported to have a statistically significant association with survival were tabulated. Whether the factor was statistically significant using univariate or multivariate analysis, or both, was documented. These factors were then qualitatively described. Some factors were reported in the original studies with a specific numeric cut-off value (such as level of albumin or age). In the review, these were broadly categorized (increased albumin or greater age) to allow the otherwise heterogeneous data to be presented and analysed coherently.

**Results**

**Description of studies**

The searches of MEDLINE and EMBASE yielded 966 and 2327 publications, respectively. The combination of these searches produced 3293 manuscripts for analysis. No additional studies were identified after reference searching. After excluding duplicate studies, studies that repeated previously published data and studies that did not include the absolute number of survivors at 10 years, 14 studies were suitable for inclusion in this review. All 14 studies were retrospective analyses. Publication dates ranged from 1987 to 2009.

**Patient characteristics**

Patient characteristics are summarized in Table 1. The total number of patients in these studies was 4197. The median patient age at study enrolment was 60 years (range: 50–64 years). Overall, 84.3% (2811 of the 3335 patients for whom data on sex were provided) of the patients were male and 78.1% (2052 of the 2626 patients for whom cirrhosis data were provided) had cirrhosis. Patient characteristics were often collated after censorship had been applied and therefore were not reflective of the initial patient population.

**Study heterogeneity**

There were significant variations in the populations included in the studies. Many of the studies included only patients with well-preserved liver function. Fukuda et al. included only patients with Child–Pugh class A liver function who underwent curative resection, whereas Lee et al. did not perform resection in patients with ‘evidence of hepatic decompensation’. The criteria for inclusion in the study by Pandey et al. were a lesion of ≥ 10 cm and Child–Pugh class A liver function. Chen et al. exclusively studied people with lesions measuring >10 cm and Child–Pugh class A or B liver function; neither Chen et al. nor Nagasue et al. performed analysis of prognostic factors after 10 years. The 2003 study by Zhou et al. was limited to HCC tumours of >10 cm, whereas their 2001 study referred to HCC measuring > 5 cm. Both Shimada et al. and Hanazaki et al. limited their analysis to patients who underwent potentially curative hepatectomy, but Shirabe et al. did not place any restrictions on patient selection.

**Primary study outcome**

The number of patients in each study and the actual and actuarial survival percentages are summarized in Table 2. Of the 4197 patients included in the analysis, 303 patients were alive at 10 years, which equates to an actual 10-year survival rate of 7.2%. Actuarial survival figures in these studies ranged from 10.5% to 46.3%. The overall rate determined across the 14 studies was 26.8%. Four studies indicated the proportion of patients whose fate at 10 years (whether dead or alive) was known. These four studies included data pertaining to 862 patients, the 10-year outcome of 750 (87.0%) of whom was known (Table 2). Eleven studies stated the rate of perioperative mortality within 3 months of surgery. In these, overall perioperative mortality was 5.0% (196 of 3912 patients). The difference between actual and actuarial survival was calculated for each study (Table 2) in order to determine whether associations could be discerned between a large difference in survival measures and country of origin of study, prevalence of cirrhosis, perioperative mortality or completeness.
Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>City and country of institution</th>
<th>Patients, n</th>
<th>Gender, male : female</th>
<th>Age, years, median</th>
<th>Age, years, mean</th>
<th>Cirrhosis, + : −</th>
<th>HBs Ag, + : −</th>
<th>HCV Ab, + : −</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fortner &amp; Fong</td>
<td>2009</td>
<td>New York, USA</td>
<td>70</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td>Pandey et al.</td>
<td>2007</td>
<td>Singapore</td>
<td>166</td>
<td>143 : 23</td>
<td>55</td>
<td>a</td>
<td>80 : 86</td>
<td>131 : 35</td>
<td>3 : 163</td>
</tr>
<tr>
<td>Hashimoto et al.</td>
<td>2007</td>
<td>Fukuoka, Japan</td>
<td>91</td>
<td>66 : 19</td>
<td>61</td>
<td>a</td>
<td>16 : 69</td>
<td>64 : 21</td>
<td></td>
</tr>
<tr>
<td>Shimada et al.</td>
<td>2005</td>
<td>Tokyo, Japan</td>
<td>578</td>
<td>383 : 98</td>
<td>a</td>
<td>60</td>
<td>75 : 406</td>
<td>286 : 144</td>
<td></td>
</tr>
<tr>
<td>Chen et al.</td>
<td>2004</td>
<td>Wuhan, China</td>
<td>525</td>
<td>471 : 54</td>
<td>37</td>
<td>a</td>
<td>480 : 45</td>
<td>366 : 159</td>
<td></td>
</tr>
<tr>
<td>Zhou et al.</td>
<td>2003</td>
<td>Shanghai, China</td>
<td>621</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td>Zhou et al.</td>
<td>2001</td>
<td>Shanghai, China</td>
<td>1 000</td>
<td>881 : 119</td>
<td>50</td>
<td>a</td>
<td>888 : 112</td>
<td>721 : 218</td>
<td></td>
</tr>
<tr>
<td>Hanazaki et al.</td>
<td>2000</td>
<td>Matsumoto, Japan</td>
<td>386</td>
<td>293 : 93</td>
<td>64</td>
<td>63</td>
<td>202 : 184</td>
<td>86 : 300</td>
<td>172 : 214</td>
</tr>
<tr>
<td>Shirabe et al.</td>
<td>1998</td>
<td>Fukuoka, Japan</td>
<td>142</td>
<td>81 : 15</td>
<td>a</td>
<td>56</td>
<td>72 : 31</td>
<td>16 : 87</td>
<td></td>
</tr>
<tr>
<td>Lee et al.</td>
<td>1996</td>
<td>Taiwan</td>
<td>48</td>
<td>42 : 6</td>
<td>a</td>
<td>55</td>
<td>40 : 8</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td>Nagasue et al.</td>
<td>1993</td>
<td>Izmo, Japan</td>
<td>229</td>
<td>188 : 41</td>
<td>a</td>
<td>61</td>
<td>177 : 52</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td>Choi et al.</td>
<td>1990</td>
<td>Hong Kong</td>
<td>174</td>
<td>147 : 27</td>
<td>a</td>
<td>54</td>
<td>113 : 56</td>
<td>132 : 42</td>
<td></td>
</tr>
<tr>
<td>Sesto et al.</td>
<td>1987</td>
<td>Cleveland, USA</td>
<td>12</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>4 197</td>
<td>2 811 : 524</td>
<td>55.9 ± 4.2</td>
<td>2 052 : 574</td>
<td>1 572 : 1 428</td>
<td>593 : 583</td>
<td></td>
</tr>
</tbody>
</table>

aThis information was analysed after the exclusion of some patients and therefore does not reflect the total patient number.
bThe analysis of patient characteristics was either incomplete or made after the exclusion of some patients and therefore does not reflect the total patient number or the initial patient population.
cMean of mean ages ± standard error of the mean.
HBs Ag+, positive hepatitis B surface antigen; HCV Ab+, positive hepatitis C antibody.

Table 2 Survival data across the 4197 patients included in the 14 studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients, n</th>
<th>10-year survivors, n</th>
<th>Patients accounted for at 10 years, n (%)</th>
<th>Perioperative mortality within 3 months, n (%)</th>
<th>Actual survival, %</th>
<th>Quoted actuarial survival, %</th>
<th>Difference between actual and actuarial survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fortner &amp; Fong</td>
<td>70</td>
<td>15</td>
<td>NS</td>
<td>9 (12.9)m</td>
<td>21.4</td>
<td>24.0</td>
<td>2.6</td>
</tr>
<tr>
<td>Fukuda et al.</td>
<td>145</td>
<td>29</td>
<td>NS</td>
<td>145 (100)</td>
<td>20.0</td>
<td>26.9</td>
<td>6.9</td>
</tr>
<tr>
<td>Pandey et al.</td>
<td>166</td>
<td>4</td>
<td>NS</td>
<td>4 (3.0)m</td>
<td>2.4</td>
<td>25.6</td>
<td>23.2</td>
</tr>
<tr>
<td>Hashimoto et al.</td>
<td>91</td>
<td>19</td>
<td>NS</td>
<td>89 (97.8)</td>
<td>3 (3.3)m</td>
<td>22.4</td>
<td>b</td>
</tr>
<tr>
<td>Shimada et al.</td>
<td>578</td>
<td>105</td>
<td>NS</td>
<td>468 (80.9)</td>
<td>18 (3.1)m</td>
<td>18.2</td>
<td>21.8</td>
</tr>
<tr>
<td>Chen et al.</td>
<td>525</td>
<td>15</td>
<td>NS</td>
<td>14 (2.7)m</td>
<td>2.9</td>
<td>b</td>
<td>b</td>
</tr>
<tr>
<td>Zhou et al.</td>
<td>621</td>
<td>11</td>
<td>NS</td>
<td>28 (4.5)m</td>
<td>1.8</td>
<td>17.5</td>
<td>15.7</td>
</tr>
<tr>
<td>Zhou et al.</td>
<td>1 000</td>
<td>60</td>
<td>NS</td>
<td>15 (1.5)m</td>
<td>6.0</td>
<td>46.3</td>
<td>40.3</td>
</tr>
<tr>
<td>Hanazaki et al.</td>
<td>386</td>
<td>7</td>
<td>NS</td>
<td>27 (7.0)m</td>
<td>1.8</td>
<td>10.5</td>
<td>8.7</td>
</tr>
<tr>
<td>Shirabe et al.</td>
<td>142</td>
<td>12</td>
<td>NS</td>
<td>39 (27.5)m</td>
<td>8.5</td>
<td>11.7</td>
<td>3.3</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>48</td>
<td>15</td>
<td>NS</td>
<td>48 (100)</td>
<td>31.0</td>
<td>b</td>
<td>b</td>
</tr>
<tr>
<td>Nagasue et al.</td>
<td>229</td>
<td>2</td>
<td>NS</td>
<td>24 (10.5)m</td>
<td>0.9</td>
<td>19.4</td>
<td>18.5</td>
</tr>
<tr>
<td>Choi et al.</td>
<td>174</td>
<td>8</td>
<td>NS</td>
<td>23 (13.2)m</td>
<td>4.6</td>
<td>b</td>
<td>b</td>
</tr>
<tr>
<td>Sesto et al.</td>
<td>22</td>
<td>1</td>
<td>NS</td>
<td>NS</td>
<td>3.5</td>
<td>12.0</td>
<td>8.6</td>
</tr>
<tr>
<td>Total</td>
<td>4 197</td>
<td>303</td>
<td>87.0</td>
<td>4.9%</td>
<td>7.2 ± 9.9</td>
<td>26.8 ± 10.5&lt;sup&gt;®&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Pperioperative mortality excluded from actuarial survival calculation.
<sup>b</sup>Actuarial survival not quoted.
<sup>c</sup>Analysis of perioperative mortality with respect to actuarial survival calculation not stated.
<sup>d</sup>Pperioperative mortality included in actuarial survival calculation.
<sup>e</sup>Overall actuarial survival calculated from studies in which these data were provided or could be calculated.
NS, not stated or cannot be derived from data presented.
of follow-up for 10 years. However, the data were insufficient to reliably describe any such patterns.

**Secondary study outcomes**

Univariate analysis demonstrated a number of patient, tumour and treatment prognostic factors associated with survival outcomes. Patient factors associated with survival outcomes are described in Table 3. Tumour and treatment factors are outlined in Tables 4 and 5, respectively. On multivariate analysis the following factors showed a positive association with survival: the absence of or a less severe stage of cirrhosis; female sex; lower serum $\gamma$-glutamyl transpeptidase ($\gamma$-GPT); lower serum bilirubin; non-cancerous liver parenchyma; higher serum albumin; a lower indocyanine green retention rate at 15 min (ICG15), and younger age.\(^9\)\(^{11}\)\(^{15}\)\(^{16}\)^19 Significant positive prognostic tumour factors were: the absence of satellite lesions; the absence of intrahepatic metastases, vascular invasion or portal vein invasion, and the absence of capsular invasion.\(^9\)\(^{11}\)\(^{15}\)\(^{16}\)^19 The only significant treatment factor, on multivariate analysis, was resection margin, whereby a margin of >10 mm was associated with a better prognosis.\(^10\)

**Discussion**

This review identified an overall 10-year actual survival rate following resection of HCC of 7.2%, which is lower than the actuarial figures quoted in the studies to which the review refers. The difference may be understood by considering the way in which actuarial survival is calculated. It is a result of subset analysis and censorship of outcomes for certain patients. For example, in the study by Shimada et al., 578 patients underwent potentially curative hepatectomy for HCC.\(^16\) Of these, 97 patients were excluded from the final analysis as seven died in hospital, 11 died within 1 month of surgery, 14 died from non-cancer causes, eight were lost to follow-up and 57 underwent palliative resection. This gives a surgical mortality of 3.1% (18/578 patients). The number of patients alive at 10 years after resection was 105, giving an actu-
rial survival percentage of 21.8% (105/481 patients). The actual survival as indicated by the number of patients alive at 10 years divided by the initial number of patients enrolled was 18.2% (105/578 patients). By excluding patients who suffered postoperative mortality and those who died from other causes, the survival quoted in these manuscripts reflects survival probability only if a patient did not die perioperatively, did not die from other causes and did not undergo the conversion of a curative to a palliative procedure once the operation had commenced and the extent of disease had been discovered. The actuarial survival figure is thus not reflective of true 10-year survival in all patients who underwent initial resection.

The actual survival outcomes in this study are reflective of a worst-case scenario, as only patients who were proven to be alive at 10 years were deemed to be actual 10-year survivors. Patients who were lost to follow-up or who were alive at the conclusion of the study but had not been followed up for 10 years were not included in the final analysis of actual survival, which may lead to an overestimation of mortality. In the actuarial survival calculations, these patients are censored and are assumed to have the same survival prospects as those who continued under follow-up. This may lead to an overly optimistic estimate of survival. In only four studies was the comprehensiveness of 10-year follow-up stated. In these, the fate of 87.0% of patients was known at 10 years. Given that these data were available for fewer than one quarter of the cohort in this analysis, the extent to which the difference between actual and actuarial survival can be accounted for by incomplete follow-up is unknown. Nevertheless, most studies censored data for reasons other than incomplete follow-up, such as perioperative mortality or death from other causes. It is likely that the most accurate survival figure will lie somewhere between the pessimistic calculation of actual survival and the optimistic actuarial survival figures that are more widely quoted.

It was not possible to perform a meta-analysis of the data in these studies because of the heterogeneous nature of the patient populations, differing qualities of outcome reporting and the lack of individual patient data provided in the manuscripts. No reliable conclusions could be drawn when the studies were analysed according to the difference between actual and actuarial survival to determine whether there might be an association with a wide range in this outcome and comorbid cirrhosis, perioperative mortality or completeness of follow-up to 10 years. This analysis was made impossible by the incomplete reporting of data in each category and the small number of studies. It may be that a large proportion of the difference reflects censorship resulting from incomplete follow-up. However, in the studies that reported these data, the vast majority (87.0%) of patients were followed until death or 10 years post-surgery.

It should be noted that there was a lack of agreement regarding the prognostic significance of many patient, tumour and treatment factors. In particular, factors determined on univariate analysis as not significant in some studies were found by others to be significant on multivariate analysis. An example of this is female sex. Fukuda et al. found it to be a positive factor on multivariate analysis, but four studies deemed female sex to be non-significant on univariate analysis. These differences make it difficult to assess the true significance of factors in relation to survival. Further long-term follow-up and multicentre analysis are required to better define survival outcomes and factors with prognostic significance. In order to distinguish the effect of HCC from that of its common comorbidity, cirrhosis, it would be necessary to perform cohort studies with age- and disease-matched controls. Prognostic factors could then be increasingly considered in planning treatment for patients.

Actual long-term survival after resection of HCC is poorer than the actuarial figures reported imply. The significance of the difference between actuarial and actual survival data pertains to the expectations of clinicians and patients when discussing treatment options. Although Kaplan–Meier survival analysis is a legitimate and necessary tool for providing survival estimates, especially when comparing groups in controlled clinical trials, for most patients and many clinicians it can lead to a significant overesti-

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**Table 5** Univariate analysis of prognostic treatment factors

<table>
<thead>
<tr>
<th>Study</th>
<th>Preoperative</th>
<th>Resection: limited vs. anatomical</th>
<th>Surgical margin positive</th>
<th>Blood transfusion</th>
<th>Blood loss (higher)</th>
<th>Resection intent: curative vs. palliative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fukuda et al.</td>
<td>NS</td>
<td>NS</td>
<td>5 mm NS</td>
<td>NS</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td>Pandey et al.</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>a</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td>Hashimoto et al.</td>
<td>a</td>
<td>a</td>
<td>NS</td>
<td>NS</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td>Shimada et al.</td>
<td>NS</td>
<td>NEG</td>
<td>NEG</td>
<td>a</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td>Zhou et al.</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>POS</td>
</tr>
<tr>
<td>Zhou et al.</td>
<td>a</td>
<td>NS</td>
<td>NEG</td>
<td>a</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td>Hanazaki et al.</td>
<td>NS</td>
<td>NS</td>
<td>&gt;5 mm POS</td>
<td>a</td>
<td>NEG (&gt;1500 ml)</td>
<td>a</td>
</tr>
<tr>
<td>Shirabe et al.</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
<td>a</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>a</td>
<td>a</td>
<td>&gt;10 mm POS</td>
<td>a</td>
<td>a</td>
<td>a</td>
</tr>
</tbody>
</table>

aAnalysis not performed or not specifically identified.
NS, not significant; POS, positive prognostic factor; NEG, negative prognostic factor; TACE, transarterial chemoembolization.
mation of the utility of treatment and likely outcomes of surgery. A patient who is informed that she has a 20% chance of survival for 10 years post-surgery is unlikely to interpret this as meaning that she has a 20% chance of survival only if she does not die perioperatively, does not die from other diseases and if her curative procedure is not deemed palliative once the operation commences. The actual survival rate is the more intuitive and appropriate measure to use when discussing treatment options with patients.

Conflicts of interest
None declared.

References

Appendix A1

Search strategy for MEDLINE
1 exp hepatectomy/ (19 350)
2 liver resection.mp. (4278)
3 exp carcinoma, hepatocellular/ (51 560)
4 exp disease-free survival/ or exp survival/ or exp survival rate/ (137 147)
5 ten-year survival.mp. (640)
6 or 5 (137 607)
7 1 or 2 (20 865)
8 3 and 7 (3909)
9 6 and 8 (968)
10 limit 9 to humans (966)

Search strategy for EMBASE
1 exp liver resection/ (28 236)
2 exp liver cell carcinoma/ (67 745)
3 exp overall survival/ or exp survival/ or exp event-free survival/ (415 045)
4 ten-year survival.mp. (705)
5 hepatocellular carcinoma.mp. (45 885)
6 hepatectomy.mp. (15 749)
7 1 or 6 (31 418)
8 2 or 5 (74 349)
9 7 and 8 (6795)
10 3 or 4 (415 304)
11 9 and 10 (2566)
12 limit 11 to human (2327)