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ESSAY

Stem cell replication, somatic mutations and role of randomness in the development of cancer

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Abstract

An intense scientific debate has recently taken place relating to the "bad luck" hypothesis in cancer development, namely that intrinsic random, and therefore unavoidable, mutagenic events would have a predominant role in tumorigenesis. In this article we review the main contributions to this debate and explain the reasons why the claim that cancer is mostly explained by intrinsic random factors is unsupported by data and theoretical models. In support of this, we present an analysis showing that smoking-induced mutations are more predictive of cancer risk than the lifetime number of stem cell cellular divisions.

Keywords Environment · Epidemiology · Cancer · Somatic mutations · Risk factors

Introduction

Tomasetti and Vogelstein have recently published a number of papers [1–5] in which they discuss the strong correlation observed between lifetime cancer risk and the total number of divisions in normal stem cells as estimated by a mathematical method they developed. The two authors advanced the thesis that the causes for this correlation are the driver gene mutations that randomly occur during these divisions and represent the necessary events that lead to cancer, thus suggesting that an intrinsic and unavoidable stochastic risk factor has a major role in cancer development. This thesis was summed up in the abstract of the 2015 Science article by the provocative sentence «The majority [of cancers] is due to bad luck» and made the headlines of scientific journals as well as the general press, where it was reformulated in controversial titles such as «The bad luck of cancer» (Science, 2 January 2015), «Most cancers arise from bad luck» (Scientific American, 24 March 2017), and «Cancer random's assault» (The New York Times, 5 January 2015). Such formulations of Tomasetti and Vogelstein's work misrepresent their original findings, may have potentially important implications for primary prevention policies and have caused a reaction through many commentaries and research papers. In this article, we will briefly summarize the original findings together with the principal criticisms that followed and we produce an original analysis suggesting that stem cell divisions are poorly predictive of smoking-related risk.

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Cancer risk explained by the number of stem cell divisions

In the first paper of the series, the two authors proposed a mathematical model for the number of lifetime stem cell divisions (LSCD) as a function of two parameters: the number s of stem cells found in fully developed tissues and the total number d of divisions each of these cells undergo in the lifetime of an individual. Importantly, by construction LSCD estimates do not account explicitly for specific genetic and environmental factors (other than the ones possibly affecting s and d in a *systematic* fashion). After estimating LSCD for 25 different tissues for which data about the parameters are available, they showed that the sample correlation between lifetime cancer risk (CR) in the US and the LSCD in a log–log scale is 0.81, Fig. 1. By means of parametric simulations, this correlation was found to be very robust to errors in LSCD estimates. More surprisingly, Tomasetti et al. [5] in an updated analysis showed that similar correlations can be found using CR figures for each of 68 different countries, thus addressing concerns of many researchers [6–11] and by an IARC press release [12].

A correlation of 0.81 implies that the proportion of the variation of log(CR) explained by log(LSCD) is $R^2 = 0.66$ [$= 0.81^2$]. This became the justification for the claim that 2/3 of cancers *are due* to *intrinsic* and unpreventable causes, that is "bad luck". There are two important reasons why this interpretation is controversial. First, this is a purely statistical analysis, so by comparing the CR and LSCD of different tissues, only an *ecological* correlation can be derived [13], that is nothing can be inferred about the probability for an *individual* to develop cancer in a given tissue given his/her LSCD (which, incidentally, is unknown).

Secondly, it is not possible to give a straightforward interpretation of such a correlation in terms of fraction of risk attributable to some etiological factor. To understand this Weinberg and Zaykin [13] and Wu et al. [14] proposed the following thought experiment: imagine introducing a hypothetical carcinogenic agent in the environment that doubles the risk of all cancers and the whole population is exposed to it. In this situation, one half of the cancers would

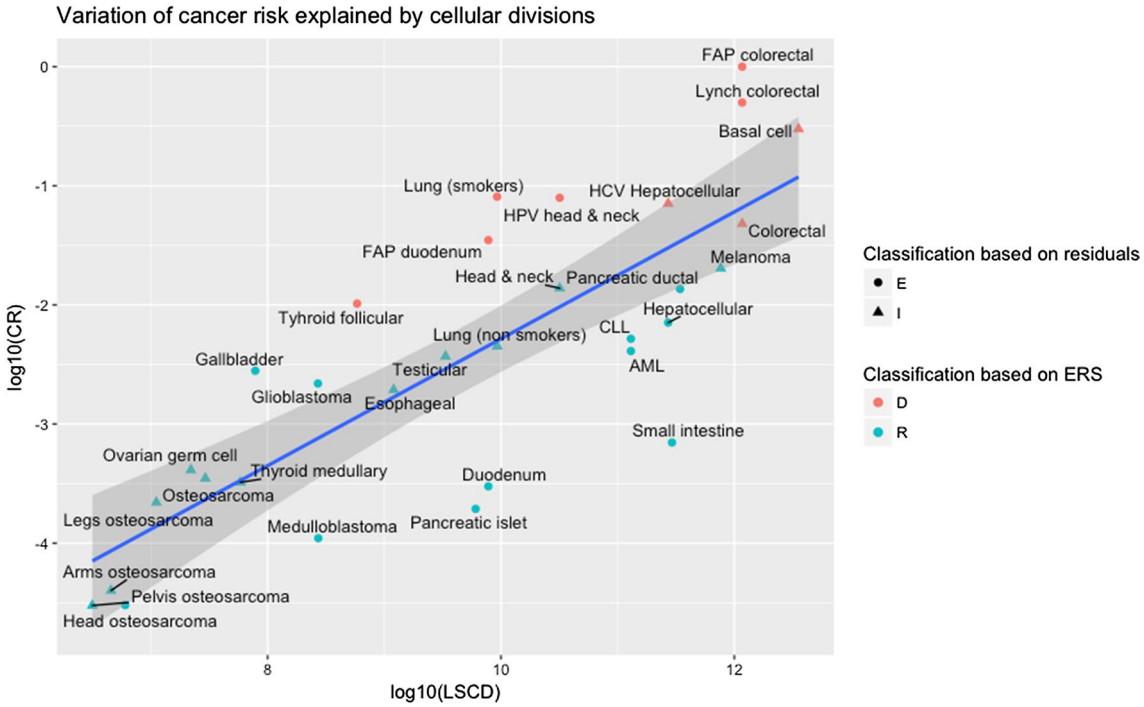

Fig. 1 Linear regression analysis of lifetime stem-cell divisions and cancer risk of tissues. Data are from figure 1 of the 2015 Science paper by Tomasetti and Vogelstein [1]. Pearson correlation is 0.81, implying that $R^2 = 0.65$ of the risk differences among tissues is explained by variation in cell divisions. Shaded area represents the 95% confidence interval for the risk predicted by the linear model. In one over many possible interpretations, triangular dots in this area can be considered as representing *intrinsic* cancers, that is cancers mainly due to unavoidable replicative mutations, while for all other cancers harmful (dots above the area) or protective (dots below the area) *extrinsic* factors have a major role. An alternative classification was done by Tomasetti and Vogelstein based on a hierarchical modeling of cancers according to their *Extra Risk Score*. According to this classification, replicative cancers are in blue and extrinsic (i.e. *deterministic*) cancers are in red

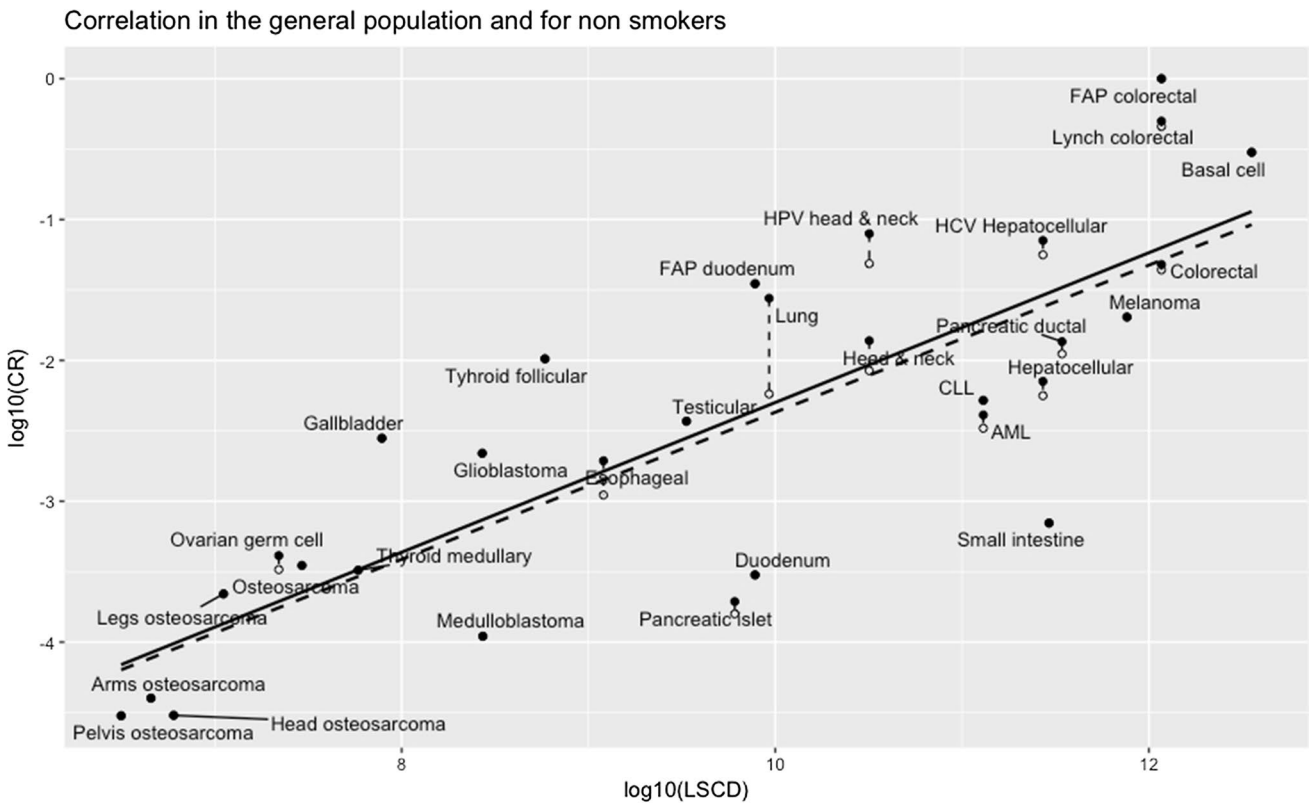

Fig. 2 Linear regression analysis of lifetime stem-cell divisions and cancer risk of tissues in the general population (continuous line) and for non-smokers (dashed line). For tobacco related cancers, a vertical dashed segment connects the dots representing the two risks. Risks for non-smokers were calculated by combining hazard ratio estimates from Agudo et al. [15] and lifetime cancer risk from Tomasetti and Vogelstein [1] and considering a smoking prevalence of 0.3. For both the general population and non-smokers, the correlation is 0.81

be attributable to the exposure to this powerful agent while the correlation between log(CR) and log(LSCD) would not change, because coordinates (log(CR), log(LSCD)) have been simply shifted upward by the constant log(2).[1] A more realistic illustration of this phenomenon can be seen in Fig. 2. Even though for tobacco related cancer types, more than 30% of new cases could be prevented by eliminating smoking [15], the correlation between log(LSCD) and log(CR) does not change if instead of considering overall lifetime risk, one considers lifetime risk for non-smokers.

The previous example shows that the observed correlation may not be in contradiction to a large number of epidemiological findings showing that environmental factors have a major role in many cancers. Yet, implicit in the ambiguous formulation that 2/3 of cancers are due to intrinsic unpreventable factors, is the idea that the remaining 1/3 of cancers are due to genetic hereditary and environmental factors, that is to *extrinsic* factors. This inference would be incorrect, as it is not possible to partition the etiological determinants of a disease so that their relative effects add up to 1. This problem is well known and has been described in several papers [10, 13, 16–18]. In this context, it is reasonable to assume that environmental and genetic factors have an indirect effect on cancer risk that may be possibly mediated by the number of cellular divisions *d*. The modeling hypothesis assuming that *d* is independent of environmental and genetic factors is therefore unrealistic.

Classification of tumors

In a first attempt to discriminate between intrinsic replicative (R) and extrinsic environmental (E) and hereditary (H) factors, the 2015 paper introduced a score to classify tumors according to the importance of these factors in their development. The *Extra Risk Score* (ERS) of a tissue is simply defined as the product log(LSCD) x log(CR). According to its authors, a higher ERS points toward a relative more important role of E and H factors.

[1] This is a hypothetical example. In their 2017 paper Tomasetti et al. [5] argued that there is not evidence that a single environmental factor is able to increase the risk of cancer of each tissue proportionally to its total number of stem cell divisions, not even exposure to radiation following the atomic bombing of Hiroshima and Nagasaki.

As pointed out by several authors, the definition of this score is unconvincing, in particular the choice of a product (as opposed to a ratio). And indeed, had we to stay in the original linear regression framework, it would be more reasonable to consider as intrinsic those cancers whose risk is well predicted by LSCD, that is those that are close to the straight line regressing log(CR) against log(LSCD). All other cancers, further away from this line, could then be considered as extrinsic, Fig. 1. Note that according to this definition, some cancers have a lower incidence than the one predicted by the number of cellular divisions, as if protective environmental or hereditary factors were systematically at play. Wu et al. [14] take a complementary approach in which extrinsic effects can only contribute to increase risk and thus argue that in order to infer the intrinsic risk regression line, only cancers with lower risk should be considered. Accordingly, the intrinsic line is fitted on the lowest boundary of Fig. 1 and all cancers above it are considered as extrinsic. This approach seems unrealistic as it rules out factors that systematically lead to decreased risk such as, say, fiber intake in colorectal cancer.

Proportion of mutations due to replicative mechanisms

The confusion around the relative contributions of intrinsic and extrinsic factors was explicitly addressed by Tomasetti et al. in their 2017 Science paper where a clear conceptual distinction was made between the proportion of preventable cancers and the proportion of driver mutations due to E, thus clarifying what the authors meant by a major role of R in cancer development. This crucial distinction is best understood by means of another simple thought experiment. Imagine a cancer type that requires three driver mutations to develop. If 2/3 of the driver mutations are contributed (on average) by intrinsic R and 1/3 by extrinsic E, then 100% of cases could be prevented by removing E. Tomasetti et al. developed a method for estimating the proportions of driver gene mutations due to E, H and R based on cancer sequencing and epidemiological data; however as above, partitioning cause in this way is in principle impossible. Sequencing allows the estimation of the number of mutations due to R in unexposed samples and the total number of mutations in exposed samples. If sequencing data are not available, they propose conservative estimates of the proportion of driver mutations due to R based on epidemiological data and on a priori knowledge of the number of driver mutations required for cancer onset.

This model allows the parameterization of the proportion of preventable cancers as a function of the proportion of driver mutations due to E (together with the relative risk and the prevalence of E). Crucially, this model implies that the latter is always less than the former. For instance, the proportions of driver mutations due to E, H, and R in lung cancers are respectively 0.661, 0.005, and 0.334, while the proportion of preventable cases is 0.89. Mesothelioma has similar proportions, while the proportion of attributable risk due to asbestos exposure for men is as high as 0.97 [19]. Note that by definition, the former proportions add up to one contrary to the latter epidemiological notion of attributable fraction.

Kelly-Irving et al. [20] explain the discrepancy between the proportion of risk not amenable to extrinsic factors and the proportion of driver mutations due to R in the context of the hallmarks of the cancer paradigm. They argue that while necessary, mutations are not sufficient for cancer development as they must be accompanied by other (i.e. non-genotoxic) cellular systems dysfunctions, notably in the immune system [21, 22].

Evidence exists that some carcinogenic compounds such as asbestos increase cancer risk (i.e. risk of mesothelioma in the case of asbestos) through both mutagenic actions (i.e. direct genetic changes) and non-mutagenic actions (e.g. increase in cell proliferation leading to the accumulation of mutations) [23].

In conclusion, if we must refer to «bad luck», that is "unpreventability", the appropriate way to formulate it would be with reference to the total driver mutation load rather than to the development of the disease. While this distinction is more difficult to communicate to the general public, that is unlikely to know much about carcinogenesis, it is of the greatest importance for counterbalancing dangerous previous claims about cancer ineluctability.

Alternative data-driven estimation of proportion of intrinsic mutations

Wu et al. [14] suggested an alternative method to estimate the proportions of mutations due to intrinsic and extrinsic factors based on mutational signatures. These are patterns of mutations resulting from mutagenic processes leaving marks on the genome according to their intensity; the mutational load of a cancer genome can be seen as the (weighted) sum of several signatures. Signatures can be extracted from sequencing data by means of matrix factorization algorithms. Large-scale analysis have so far identified around 30 signatures among all types of cancers [24], listed in the Catalogue Of Somatic Mutations In Cancer (COSMIC) database.[2] Several of these signatures have been found associated to specific exposures [25]. Remarkably, COSMIC signature 1 has been found to correlate with age at cancer diagnosis.

[2] http://cancer.sanger.ac.uk/cosmic/signatures.

Wu et al. suggested exploiting this property and considering the relative contribution of signature 1 to the total mutational load of a genome as a proxy for its proportion of intrinsic mutations. The remaining mutations are considered as extrinsic with known or unknown etiology. Using data from Alexandrov et al. [24], Wu et al. estimated that in most cancer types the vast majority of mutations (70–90%) is due to extrinsic factors. Estimates are in some cases very different from the ones by Tomasetti and colleagues: for instance, intrinsic factors would account for 14.2% of driver mutations required for bladder cancer development, whereas Tomasetti et al. estimate is 76%.

A critical assumption behind this method (and the model developed by Tomasetti et al.), is that driver mutations form a *representative sample* of all somatic mutations in a cancer genome that is possible to measure through sequencing, so that the proportions of all somatic mutations due to intrinsic and extrinsic factors are equal to the corresponding proportions of driver mutations. This important point went underappreciated in the commentaries following the original publications and is particularly difficult to appreciate.

Wu et al. also developed a Galton-Watson branching-process model [26] to calculate the lifetime risk as a function of the number of cell divisions for different values of the number of driver mutations required to form cancer. By comparing this theoretical line with the regression line they use to discriminate purely intrinsic cancer and other cancer they conclude that Tomasetti et al. overestimate the role of intrinsic factors. Little and Hendry [27] generalized this approach to a more realistic theoretical model and showed a significant correlation between the probability of a cancer being mutagen induced and the total number of stem cell divisions.

Empirical evidence that extrinsic mutations are more predictive of cancer risk than number of cellular divisions in lung cancer

As we argued, the claims by Tomasetti and Vogelstein about a putative predominant role played by random mechanisms in the development of cancer needs to be interpreted in terms of the contribution of such mechanisms to the load of driver mutations rather than to cancer risk. From this point of view, it is plausible that highly preventable cancers exist where intrinsic factors are responsible for the majority of the driver mutations. Obviously, the alternative (and more immediate) situation of preventable cancers where mutations due to environmental exposure are highly predictive of risk is also possible and here we give further evidence of it.

Based on previous research [15, 28] we estimated the mutation rates caused by tobacco smoking in smokers, in different types of tissues, and compared them with stem cell lifetime divisions for the same tissues when available in Tomasetti and Vogelstein's work (Table 1). We compared both measures with cancer incidence hazard ratios or mortality rates in smokers and non-smokers in the same tissues. As we show in Table 1, the correlation between mutation rates in the cells of smokers and cancer incidence

Table 1 Comparison between mutation rates, cumulative stem cell lifetime divisions, hazard ratios for cancer in smokers and mortality rates in smokers and never smokers, for the cancer sites for which information was available in all sources

Cancer site	Mutation rates in smokers[a]	Cumulative stem cell lifetime divisions[b]	Incidence hazard ratio (relative risk) for smoking men[c]	Incidence hazard ratio (relative risk) for former smoking men[c]	Mortality rates smokers with ≥ 25 cigarettes/day/non-smokers[d]
Lung adenocarcinoma	150.5	9.272×10^{9} [e]	23.30	5.28	415.2/16.9
Larynx	137.7	3.186×10^{10} [f]	13.24	3.51	17.3/0
Pharynx	38.5	NA	6.67	2.06	19.4/0
Bladder	18.3	NA	3.84	2.15	51.4/13.7
Esophagus (squamous)	N.S.	1.203×10^{9}	3.94	1.26	50.0/5.7
Liver	6.4	2.709×10^{11}	2.92	2.09	31.3/4.4
Pancreas adenocarcinoma	N.S.	3.428×10^{11}	1.62	0.89	52.9/20.6

[a]Statistically significant average number of somatic substitutions per genome per pack-year. From Alexandrov et al. [28]

[b]Cumulative number of divisions of stem cells per lifetime. From Tomasetti and Vogelstein [1]

[c]From Agudo et al. [15]

[d]Cumulative mortality rate per 100,000 persons per year, from Doll et al. [35]

[e]Cumulative number of divisions of stem cells per lifetime. From Tomasetti and Vogelstein [1]

[f]Adenocarcinoma (same rate in smokers and non-smokers)

hazard ratios for smokers relative to non-smokers is much more evident than the association of the latter with stem cell lifetime divisions. The correlation coefficient for the association between the cancer incidence hazard ratio for smokers and mutation rates (per pack year) in smokers is $\rho = 0.93$, with a significant trend ($p = 0.0207$). The correlation coefficient is $\rho = -0.65$ when we compare the cancer incidence hazard ratio with cumulative stem cell divisions, with a non-significant negative trend ($p = 0.2319$). The pattern for former smokers is similar, with the correlation between the cancer incidence hazard ratios and mutation rates (per pack year) being $\rho = 0.91$, with a significant trend ($p = 0.0330$), while cumulative stem cell divisions are only weakly negatively correlated with cancer hazard ratios ($\rho = -0.58$, $p = 0.3091$). There are similar findings when smoking mortality rate difference is employed instead of smoking-associated incidence relative risk, although all trends are non-significant ($p > 0.10$). This reinforces the results of the analysis by Little and colleagues [29] using data taken from the 2015 Science paper of Tomasetti and Vogelstein which suggested that stem cell divisions are poorly predictive of smoking-related risk.

Conclusions

In this article we reviewed the debate around the correlation between lifetime stem cell division and cancer risks, supporting the view that this correlation does not allow to distinguish between intrinsic and extrinsic cancers. Moreover, we provided an original analysis that, although based on a small number of cancer endpoints, indicates that smoking-induced mutations are more likely to be related to smoking-associated cancer risk than smoking-associated cancer risk is to cumulative stem cell lifetime divisions.

From a modeling point of view, there are several possible directions for future work. Genetics and environment are not necessarily independent of stem-cell divisions, so it would be interesting to include them in the model for estimating the number of lifetime cell divisions. For instance, it is reasonable to assume that chronic inflammation leads to increased stem cell proliferation. Another interesting perspective would be to take epigenetic events into account [30]. This would require building a model for estimating the fraction of such events in the total number of events required for cancer development. It is important to note that somatic mutations are not sufficient to cause cancer. Other events or conditions that may play an important role and that are not considered in current models are disrupted or inefficient DNA repair mechanisms, that may be limited to some organs, and dysfunctions of immune surveillance.

The articles of Tomasetti et al. have initiated intense debate around the role of chance in tumorigenesis with several commentaries and original papers published in the last 3 years. The idea that random phenomena have an important role in cancer etiology is however not new, as it was implicit in the model advanced more than 60 years ago by Armitage and Doll [31]. In this context, the results by Tomasetti and Vogelstein provide an estimate of the role of randomness on the occurrence of somatic and driver mutations and not directly on cancer occurrence. However, this distinction was lost in subsequent media coverage that opted for a catastrophic, and false, take home message ("Cancer is a matter of bad luck, therefore healthy life style makes little or no difference").

One possible reason for such misrepresentation in the media is that reporting on random phenomena is difficult because of problems in the common understanding of probability [32], in particular how probabilities of an outcome are affected by interventions (such as the effect of quitting smoking on cancer risk). One might argue that the role of chance is an epistemological feature of epidemiology: disease risks are expressed as probabilities that are usually less than one, so in principle one could always talk about "bad luck" at the individual level. Even for lung cancer, where much research has demonstrated a much higher probability of developing lung cancer in smokers than non-smokers, one can still talk about "bad luck" because the causative path from smoking to cancer is not deterministic. In conclusion, when communicating results about disease risk to the media and the general public, scientists must put extra care because in common language the terms "luck", "chance" and "random" are used in relation to events over which we have no control [33, 34].

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Author's Contribution GS and PV conceived the study. VP, GS and HO did the review and the figures. All authors designed the study, collected the data, did the statistical analysis, analysed and interpreted the data, wrote and reviewed the manuscript, and approved the final version.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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