TABLE I. Responses of students to the utility of the online quiz

Question	Likert scale responses				
	0	1	2	3	4
Did the online quiz help to cope with lockdown stress?	30.4%	43.5%	26.1%	na	na
Did the quiz interfere with your daily routine?	78.3%	21.7%	0	na	na
How often did you use the Kahoot practice mode to improve your score after the quiz?	Never: 17.4%	Only once: 52.2%	More than once: 30.4%	na	na
On a scale of 0 to 4 how much did gamification enhance your retention of the knowledge?	0	0	43.5%	39.1%	17.4%

na not available

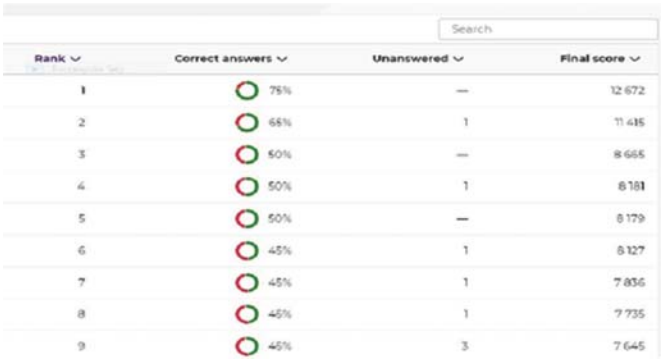

FIG 1c. An example of the final ranking of students with their scores summarized by Kahoot! at the end of the quiz

FIG 1d. An example of a podium displayed at the end of the quiz with rankings

After five sessions, the students were asked to fill an online feedback form. Twenty-three of 24 students responded to the questionnaire. All the students (23/23) found the online quiz useful (Table I).

The intervention was well-received by the students. However, during the study, some problems associated with the use of Kahoot! came to light. There was a tendency to guess among the students due to the time limit imposed and extra credits for fast responders. There was also a fear of being exposed as a low scorer due to peer pressure. Since the group consisted of students of different batches there was always a fear of being outperformed by a junior student.

Gamification cannot be for everyone and it needs to be handled with care by medical teachers. Quizzing requires an element of guesswork, hence it is important to recognize that while it is nice to encourage competition by quizzes, one should not give the impression that guessing is being encouraged. The students also need to know that the purpose of using a quiz in the classroom, whether online or offline, is to have a lively atmosphere.

A big hurdle to the virtual or online teaching model is the inconsistent availability of fast-speed internet at all locations. However, the situation is improving with better 4G penetration in small towns and tier-2 cities.The time allotted to the students for each question needs to be thoughtfully addressed. If it is too long, the students can google the question and find the answer and if it is too short, they are likely to get frustrated. More complex questions requiring analytical skills cannot be asked on Kahoot! and similar quizzing platforms.[4]

Conflict of interest. None declared

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[**To cite:** Garg N, Tanveer N, Dixit S. Student feedback on the use of gamification for teaching pathology postgraduates [Correspondence]. *Natl Med J India* 2021;**34:**375–76.]

Monoclonal gammopathy of unknown significance: Implications of Indian baseline data

Monoclonal gammopathy of unknown significance (MGUS) is one of the commonest asymptomatic pre-malignant conditions seen in the population, characterized by the presence of a monoclonal protein in the blood without any end-organ damage such as hypercalcaemia, renal injury, anaemia or bony lesions.[1] The International Myeloma Working Group (IMWG) provides criteria for diagnosis of MGUS, stating that the quantity of the monoclonal protein should be <3 g/dl, with <10% plasma cells in the bone marrow. In addition, there should not be any myeloma defining event, with urinary monoclonal protein <500 mg/dl.[1] It is well known that MGUS consistently precedes the onset of symptomatic myeloma.[2] The prevalence of MGUS is estimated at approximately 3% of the population >50 years of age, based on data from western countries.[3]

MGUS is no longer considered a disease of 'unknown significance', as all patients have a variable risk of end organ damage and progression to myeloma. The risk of progression to myeloma is approximately 1% per year, with a subset of individuals at a much higher risk.[4] Patients at the highest risk have a 58% chance of progression over 20 years, compared to 5% for low-risk patients.[5] Features such as size of the initial M spike, type of M protein and free light chain ratio enable this differentiation. Multiple scoring systems, including the Mayo score (type and quantity of M protein, FLC ratio) or the Perez Persona score (aberrant bone marrow plasma cells) allow prediction of risk of transformation to myeloma.[6]Additionally, patients with MGUS are at a higher risk of end-organ damage, such as nephropathy, neuropathy and osteoporosis, indicating a need for closer monitoring. The genetic nature of MGUS is also observed to be more complex than initially thought, with many patients having a gene expression profile similar to myeloma.[7] Certain chromosomal abnormalities such as del 17p, t(4;14), monosomy 13 and gain 1q may be present at the stage of MGUS itself and portend a higher risk of transformation.[8]

Although epidemiology of multiple myeloma (MM) is well documented from Indian centres, data on MGUS are lacking. We present a perspective on the complex nature of MGUS, including genetic and geographical differences, and highlight the need for indigenous population-based data.

MGUS is genetically heterogeneous complex condition

Primary genetic abnormalities in myeloma are unique to each clone and are now noted to arise at the stage of MGUS.[9] These have a significant impact on the initial presentation and progression. Secondary cytogenetic abnormalities arise with disease progression and clonal evolution, and are non-exclusive. Individuals with MGUS have gene expression profiling signature that is similar to malignant plasma cells. Data on the pathway of progression to myeloma are conflicting, and some studies suggest that most of the myeloma-associated mutations may be present in MGUS and malignant transformation is associated with expansion of pre-existing clones.[10] On the other hand, the presence of fewer genetic mutations in MGUS compared to myeloma favours the acquisition of new mutations for progression. In a review, Fakhri *et al.* have described possible pathways of clonal evolution in myeloma, including preferential expansion of a single clone, linear evolution or branching evolution.[11] This indicates that genetic alterations and somatic mutations are in place at the stage of MGUS. Identification of these defects in the stage of MGUS has the potential to provide valuable insights into differences in progression to myeloma and survival.

MGUS has a definite geographical variation

Geographical differences in presentation and progression of various haematological malignancies have been noted in multiple studies.[12] The most important examples of these are seen with chronic myeloid leukaemia, non-Hodgkin's lymphoma and MM, which occur in the Indian subcontinent at a much younger age.[13,14] Approximately 12% of Indian patients with myeloma present at less than 40 years of age, compared to 5% in the western population.[15] A larger proportion of patients from India are likely to have end-organ damage and advanced disease at presentation.

Such a difference in the epidemiology of MGUS has been noted in multiple studies. The prevalence of MGUS in African American populations is almost twice that of Caucasians.[16] In a large meta-analysis including studies on epidemiology of MGUS, the prevalence of MGUS ranged from 0.3 % to 6% depending on the geographical location surveyed.[17] The risk of progression to myeloma is also higher in blacks, and lowest in Japanese or Mexican populations.[18] Family history and exposure to pesticides have been associated with a higher risk of development of MGUS.[19]

With so much heterogeneity in geographical trends, it is essential to have data from India. Most epidemiological data on MGUS are from the western literature, and sparse data exist in the Indian context. The largest dataset from India is a hospital-based study from the All India Institute of Medical Science (AIIMS), New Delhi that noted an average prevalence of 1.43%, which is lower than what is reported in western data.[20] Underlying differences in genetic landscape may explain this difference in incidence and risk of progression. At present, there are no data on the genetic landscape of MGUS in the Indian setting, and very scant data are available worldwide.

Why should individuals with MGUS be identified?

The major incentive to test asymptomatic individuals for MGUS lies in the possibility of early identification and treatment of myeloma. Patients who are at high risk of progression may benefit from screening and early institution of therapy, before end-organ damage sets in.[21]

Support for routine follow up of MGUS comes from population-based studies, which indicate that patients with myeloma who have already been diagnosed to have MGUS have a lower incidence of end-organ damage and a slight overall survival advantage.[22] Current guidelines do not recommend routine population screening for MGUS and indicate testing only for symptomatic individuals. The iSTOPMM trial in Iceland is underway to evaluate the effect on screening on long-term mortality. Even in the absence of prospective evidence, there is recommendation by several guidelines to screen MGUS patients annually to detect signs of progression.[23] Theoretically, treating a patient at the stage of MGUS has the potential to 'prevent' the onset of myeloma, avoiding toxicity and the cost associated with the treatment of myeloma.[24]

Recognition of patients with MGUS has the potential to provide more insights into pathogenesis of MM. As MGUS is asymptomatic at the early stage, discovering any association with environmental exposure, certain occupations, or other pre-existing diseases can possibly help to elucidate causative influences, if any. It would also illustrate the disease pathogenesis and progression. With increasing data on MM, it is becoming clear that MM is not a single disease but consists of different genetic subtypes, each with variable clinical behaviour.[25] A simple method to do the same is to perform a serum protein electrophoresis and if feasible, immunofixation electrophoresis on either a random healthy population sample or a group of patients presenting to the hospital for evaluation. Data on genetic changes at an early pre-malignant state (MGUS) would allow correlation of the same with disease progression and response to treatment. Acquisition of new mutations with disease progression will also allow us to describe the process of clonal evolution in these patients. The most important caveat for this strategy is that genetic and prevalence data should always be generated from the local population.

Additionally, patients with MGUS have a higher rate of mortality compared to the general population, due to both progression to myeloma and other non-malignant causes such as cardiac disease, infections and renal disease.[26] Computational models have predicted that early detection of MGUS by screening and regular follow up has the potential to significantly reduce mortality due to myeloma.[27]

The potential to identify myeloma patients early and observe for progression might provide a meaningful reason to establish population screening. Understanding the genetic landscape of MGUS will enable us to identify high-risk subtypes, potentially allowing us to answer the question of observation versus early initiation of therapy for high risk patients.

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[**To cite:** Joshi K, Singh S. Monoclonal gammopathy of unknown significance: Implications of Indian baseline data [Correspondence]. *Natl Med J India* 2021;**34:**376–8.]